ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 243, 1974

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CLINICAL APPLICATIONS OF ECHOCARDIOGRAPHY IN INFANTS AND CHILDREN

by

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UPPSALA 1974

The present publication is based on studies reported in the following papers

I. Lundström, N R. Clinical applications of echocardiography in infants and children. I Investigation of infants and children without heart disease *Acta Paed Scand, 63* 23 1974

II Lundström, N R and Mortensson, W Clinical applications of echocardiography in infants and children. II Estimation of aortic root diameter and left atrial size a comparison between echocardiography and angiocardiography *Acta Paed Scand 63* 33 1974

III. Lundström, N R. and Mortensson, W Clinical applications of echocardiography in infants and children. III. Estimation of left and right ventricular size a comparison between echocardiography and angiocardiography *Acta Paed Scand, 63* 257 1974

IV Lundström, N R. Ultrasoundcardiographic studies of the mitral valve region in young infants with mitral atresia, mitral stenosis, hypoplasia of the left ventricle, and cor triatriatum. *Circulation 45* 324 1972

V Lundström, N R. Echocardiography in the diagnosis of congenital mitral stenosis and in evaluation of the results of mitral valvotomy *Circulation 46* 44 1972

VI. Lundström, N R. Echocardiography in the diagnosis of Ebstein's anomaly of the tricuspid valve *Circulation 47* 597 1973.

In the text these papers will be referred to by their roman numerals I–VI

INTRODUCTION

Working with cardiology in infants and children the advantages of a non-invasive method are easily understood. Since many years ultrasound in diagnostic cardiology in adults has been used at the University hospital in Lund because of the pioneer work made by Edler and Hertz (34). It seemed likely that its application would be useful even in infants and children and a preliminary study was performed. The results of this have been reported previously (95 100) and since they seemed promising a more systematic evaluation was carried out. The aim of this was to evaluate the clinical usefulnes of echocardiography (formerly called ultra-sound cardiography) in pediatric cardiology. The study was concentrated on examination of the mitral valve region, the tricuspid valve region and the measurement of various intracardiac distances. One part of the study was devoted to an evaluation of the reproducibility of these various measurements and to an investigation of infants and children without heart disease to form a normal material. For the intracardiac distance measurements some reference method was necessary. As such, angiocardiography was the natural choice since this method is part of the routine investigation of an infant or child with heart disease.

PRINCIPLES OF ECHOCARDIOGRAPHY

The basis of echocardiography is that sound with a high frequency (often in the range of 1–5 MHz) can be directed as a beam. This high frequency sound is generated in a piezoelectric transducer. The passage of sound through a certain medium is described by the acoustic impedance of the medium. The acoustic impedance of a medium is defined as the product of the density of the medium and the speed at which the sound passes through the medium. When an acoustic beam strikes an interface between two media with different acoustic impedances part of the sound wave is reflected and part continues through the second medium. An analysis of the reflected ultrasound is the basis for echocardiography. For a more detailed description about the physics of ultrasound and the basic principles behind echocardiography the reader is referred to other publications (27 49 75).

The transducer[1] used in the present investigation produces 1 000 soundpulses/sec and has a frequency of 2.25 MHz. The transducer acts as a sound transmitter for 1 μsec and as a sound receiver for the remaining 999 μsec until the next sound pulse is generated. The transducer is connected to a cathode ray tube. At each pulse the electron beam starts at the left side of the screen and moves to the right along the x-axis at a constant speed. Immediately after the emission of each pulse the transducer becomes inactive and is mechanically excited by the returning echoes. These echoes are thus converted into electrical signals, which are then amplified and fed to the *y* plates of the cathode-ray tube. This results in vertical deflections of the electron beam. The echo-signals are thus seen as vertical deflections on the oscilloscope screen (Fig. 1A). This presentation of the reflected echoes is called "A mode" and is the same as that used in echoencephalography. The horizontal distance between the left border of the screen and the echo-signal is a measure of the time necessary for the pulse to travel from the transducer to the reflecting surface and back again. As long as the velocity of the sound is the same in all the media it traverses, the horizontal distance between the vertical oscillations on the screen will be a measure of the distance between

[1] Ekoline 20, Smith-Kline.

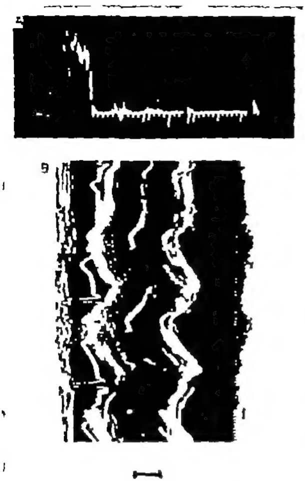


Fig 1 (A) Polaroid photographic picture of the oscilloscope screen as it is seen during scanning. The transducer was directed towards the aortic root. (B) Photographic picture of one vertical sweep of the signals from Fig. 1A after they have been converted into bright spots. An electrocardiogram is incorporated in the registration. If this picture is turned 90° clockwise the presentation is the same as in following figures.

different reflecting surfaces. As the pulse rate from the transducer is 1 000 pulses/sec, the distance between the echo-giving structures will be measured 1 000 times/sec.

If the echogiving structure moves towards the transducer the echo-signal travels along horizontal axis towards the left hand side of screen. Alternatively if the echo-giving su moves away from the transducer the echo-si moves to the right hand side of the screen Thi presentation is valuable for scanning the fie and for chosing the desired echoes. In order record on a film, the echo-signals are into bright spots along an invisible basel (intensity modulation). The strength of the is represented in this case by the brightness the spot.

The invisible baseline with the spots is upwards vertically on the oscilloscope s. Using for example a Polaroid camera a p graphic picture of the screen during one sweep shows all horizontal movements in w form (Fig. 1B). This presentation is cal "TM mode" or "M-mode" because it is a motion presentation. A single lead cardiogram is incorporated in the recordi To facilitate measurements, a time marker calibration marks representing each are recorded. When reproducing these ings it is customary to have the time axis left to right and the anterior structures in upper part of the recording. It is also poss to have this "M mode" presentation re as a continuous recording. This type of reco ing has been used extensively in recent years some investigators (40 41 42) but was available for the present investigation advantages of continuous recording when ining infants and children are obvious. U this technique it is possible to register echocardiogram while the transducer is lated, a sort of scanning technique called "M mode scanning" or "M- It has been found to be very useful for strating the anatomic relationships bet different structures (42).

REVIEW OF THE LITERATURE

For each type of investigation the review will be divided into those published before (early studies) and after (recent studies) the p investigation was started (1970).

During the last years the number of echocardiographic studies has increased rapidly All of these are not of interest with respect to pediatric cardiology and a selection has therefore been made.

The mitral valve region

Early studies For many years the main application of echocardiography was in the diagnosis and evaluation of the severity of acquired mitral stenosis in adults (27 30 31 32, 36, 67 68, 82 85, 137 169). It has been found that this diagnosis can be made by echocardiography with great accuracy The severity of the mitral stenosis can be determined as well as the mobility of the anterior mitral leaflet, and this has been found to be of great value in selecting patients for valvotomy The results of a valvotomy of the mitral valve can also be ascertained by echocardiography as well as the reoccurrence of the stenosis.

The movement of the mitral ring has been studied by echocardiography (168). This technique has also been found useful in the diagnosis of left atrial thrombosis (76) and in cases with left atrial myxoma (28 35). An abnormal movement of the anterior mitral leaflet during ventricular systole has been found in patients with hypertrophic obstructive cardiomyopathy (123, 128, 140).

Recent studies Further studies confirm the abnormal movement of the anterior mitral leaflet during ventricular systole in patients with hypertrophic obstructive cardiomyopathy (129 138 139 161) The application of this investigation to infants and children with hypertrophic obstructive cardiomyopathy has also been described (12, 13, 97). It has moreover been suggested that the outflow gradient can be determined by echocardiography in this disorder (73) and that the result of operative treatment can be evaluated by this method (3).

A syndrome with prolapse of one or both of the mitral leaflets towards the left atrium during ventricular systole has been described by several authors recently The possibility of diagnosing this syndrome by echocardiography has been shown both in adults (18, 21 87 122, 147 148) and in children (101 136) An analysis of the echocardiogram from the mitral valve region has been found to be of diagnostic value in patients with ruptured chordae tendineae (74 149) in patients with congestive cardiomyopathy and mitral regurgitation (111) and in patients with aortic regurgitation (127 153, 164).

A suggestion has been made that the echocardiogram from the mitral valve can give information about the mitral valve flow (46) and the presence of elevated left ventricular diastolic pressures (89).

In the diagnosis of acquired mitral stenosis it has been shown that the echo from the posterior mitral leaflet is of interest (25). This will be commented upon later Valvular vegetations on the mitral valve in bacterial endocarditis have been detected by echocardiography (22). The possibility of diagnosing left atrial myxoma in children by echocardiography has also been described (126).

The tricuspid valve region

Early studies The possibility of obtaining echoes from the anterior tricuspid leaflet has been known for many years (27 35) Deviations from the normal have been seen in patients with acquired tricuspid stenosis (2, 84).

The aortic root left atrium and the pulmonary artery

Early studies The possibility of obtaining echoes from the outflow tract of the left ventricle and the aortic leaflets was described early on (27 28 29) and was later followed by a more detailed study (61). The left atrium situated posterior to the aortic root was studied by echocardiography both in adults (78) and in infants and children (77). A method for measuring a left atrial dimension and calculating the left atrial volume was described (78).

Recent studies Further studies on the aortic root by echocardiography have been presented lately (62, 74 81 165) and it has been shown that it is possible to examine the pulmonary artery by echocardiography especially in younger

individuals (60). Deviations from the normal in the echocardiogram from the pulmonary artery have been found in pulmonary hypertension (115). The aortic arch and the right pulmonary artery have been examined by placing the transducer in the suprasternal notch (55), a method that was actually suggested much earlier (28)

The interventricular septum, right and left ventricle

Early studies Although echoes from the posterior left ventricular wall and the interventricular septum were identified early on (28, 29) it was not until a suggestion that the size of the right and left ventricles could be estimated by echocardiography (125) that these echoes received a greater interest.

An abnormally broad interventricular septum was demonstrated in hypertrophic cardiomyopathy (113)

Recent studies Examination of the interventricular septum and the posterior left ventricular wall, allowing investigation of the right and left ventricles has been one of the most frequently used echocardiographic applications during recent years. The width of the interventricular septum has been measured (157) and the asymmetric hypertrophy mainly involving the interventricular septum in hypertrophic cardiomyopathy has been shown by echocardiography both in adults (1 72) and in children (97). An asymmetrical septal hypertrophy has, however also been demonstrated in some patients with right ventricular hypertension (5).

An abnormal motion of the interventricular septum and signs of enlargement of the right ventricle have been demonstrated by echocardiography in patients with volume overload of the right ventricle (6 19 23 86, 102, 108, 151). An abnormal motion of the interventricular septum has also been shown in patients with left bundle branch block (103).

The main interest in the examination of the interventricular septum and the posterior left ventricular wall has been focused on measurements of left ventricular dimensions in order to measure left ventricular volumes by echocardiography (40 41 43 44 48, 52, 114 119 120, 124 130). The limitations of these applications have been discussed (121 156).

The movement of the left ventricular wall has been analysed in detail by echocardiography in order to assess the myocardial function of the left ventricle (104). Abnormalities of left ventricular wall motion have been shown in patients with congestive cardiomyopathy (15)

Pericardial effusion

Early studies The possibility of diagnosing pericardial effusion by echocardiography has received great interest. It was first described in the early years of echocardiography (76) and has later been confirmed by many authors (45 56, 88 133)

Recent studies. The use of echocardiography to detect pericardial effusion has recently been further validated both in adults (39 50, 79) and in children (37 100 118).

Congenital heart disease

Early studies In the beginning the main interest in using echocardiography in the diagnosis of congenital heart disease was concentrated to an analysis of the echocardiogram of the anterior mitral and tricuspid leaflet in cases with left to right shunt (80, 134 158) Further confirmations of these results have not appeared. The possibility of using echocardiography in the diagnosis of membraneous subaortic stenosis was also reported (158). In a preliminary report about the use of echocardiography in infants and children, deviations from the normal were found in tricuspid atresia, Ebstein's anomaly of the tricuspid valve, congenital mitral stenosis, mitral atresia and other forms of the hypoplastic left heart syndrome and in the endocardial cushion defects (95).

Recent studies Many authors have reported their experiences with echocardiographic examinations of infants and children and some of these comprise infants and children without heart disease (41 70 106, 145 151 163).

The echocardiographic examination has been

used to estimate the size of the right or left ventricle (10 106 143 144 151 163), to diagnose a single ventricle (10) mitral atresia (100 144) or aortic valvular atresia (110). The value of estimating the size of the left atrium in the diagnosis of total anomalous pulmonary venous return has been pointed out (54) This technique has also been found useful in the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery (53).

The use of echocardiographic examination of the mitral valve region in patients with atrial septal defects of primum type or atrio-ventricular canal defects has been discussed by several authors (59 100 117 162).

Regarding the tricuspid valve region echocardiography has been found to be of value in the diagnosis of tricuspid atresia (51 100) and Ebstein s anomaly of the tricuspid valve (16, 91 96, 150).

Abnormal echocardiographic findings from the aortic valve region have been reported in discrete subaortic stenosis (17 92).

The possibility of identifying the outflow vessels in transposition of the great arteries by echocardiography has recently been suggested (20, 58 146) as well as the possibility of diagnosing truncus arteriosus communis by this method (11). Trials have been made to use echocardiography in analyzing cardiac malposition complexes (109 112)

Echocardiography has been found to be useful in demonstrating the mitral-semilunar valve discontinuity in patients where both great arteries origin from the right ventricle (8). This technique has also been used to demonstrate the discontinuity between the anterior wall of the aortic root and the interventricular septum found in some patients with Fallot s anomaly (14 63 152) as well as the width of the outflow tract of the right ventricle in this anomaly (14)

Identification of intracardiac echoes

The identification of intracardiac echoes naturally received great interest in the early years of echocardiography The identification was made both by a comparison with other types of recordings (electrocardiogram, intravascular pressures etc.) (29) and by experimental investigations (27 33).

The possibility of in-vivo confirmation of the origin of intracardiac echoes by a contrast echo method was described in 1969 (64)

The problem of identification of the intracardiac echoes will be discussed in more detail below

Review articles and monographs

During the nigh on twenty years of echocardiography several review articles have appeared, both in the early years (28 29) and during recent years (9 40 63, 107) Two monographs about echocardiography have been published. The first appeared in 1970 (135) and is mainly concerned with echocardiography of the anterior mitral leaflet. The more recently published monograph (41) covers the entire field of echocardiography including a description of the technique of performing the examination.

ECHOCARDIOGRAPHIC EXAMINATION OF INFANTS AND CHILDREN WITHOUT HEART DISEASE AND INVESTIGATION OF THE REPRODUCIBILITY OF THE MEASUREMENTS (I)

A short outline of the echocardiographic examination In the echocardiographic study the following four regions were examined (1) the anterior mitral leaflet, (2) the aortic root and the left atrium, (3) the interventricular septum and the posterior left ventricular wall, and (4) the anterior tricuspid leaflet. The echocardiographic examination was started with the transducer placed in the fourth or sometimes the third left intercostal space, 2 5 cm. from the midline The character

Fig. 2. Echocardiogram of the anterior mitral leaflet (*AM*) in a child without heart disease. In this and subsequent echocardiograms the top of the figure represents the anterior direction. A schematic line drawing is included. For further explanation, see text.

istic echo from the anterior mitral leaflet (Fig. 2) was first identified. A careful search was made to obtain an echo with as large an amplitude of movement as possible from the anterior mitral leaflet. On this echocardiogram the following measurements were made: the total amplitude of movement (vertical distance between points *C* and *E* in Fig. 2), the amplitude of opening movement at the beginning of diastole (vertical distance between points *D* and *E* in Fig. 2) and the speed of posterior movement during the early part of diastole (speed of movement between points *E* and *F* in Fig. 2). The latter measurement could only be made when the part of diastole before atrial systole was long enough to allow a valid measurement, i.e. with a heart rate below 120–130/min. After satisfactory echocardiograms from the anterior mitral leaflet had been obtained the transducer was tilted so that the ultrasonic beam was directed in the superior-medial direction. With the transducer in the third or sometimes the second left inter-

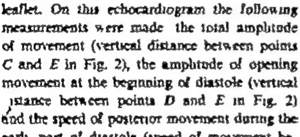


Fig. 3. Echocardiogram of the aortic root and the left atrium in a child without heart disease. The sites where the measurements of the aortic root diameter (*AOD*) and the left atrial dimension (*LAD*) were made, are indicated in the line drawing.

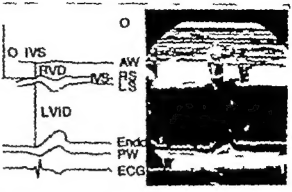


Fig. 4. Echocardiogram of the interventricular septum and the posterior left ventricular wall in a child without heart disease. The sites where measurements were made of the left ventricular internal dimension (*LVID*), the right ventricular dimension (*RVD*) and the distance between the anterior chest wall and the right side of the interventricular septum (*O-IVS*) are indicated in the line drawing. Abbreviations: *O* = anterior chest wall; *AW* = anterior wall of the right ventricle; *RS* = right side of the interventricular septum (*IVS*); *LS* = left side of the interventricular septum; Endo = endocardial posterior wall of the left ventricle; *PW* = posterior epicardial wall of the left ventricle; *ECG* = electrocardiogram.

costal space and directed in the superior medial direction the parallel echoes from the aortic root were obtained, with an echo from an aortic leaflet between them (Fig. 3). It could easily be demonstrated that the echo from the posterior wall of the aortic root was in continuity with the echo from the anterior mitral leaflet and that the echo from the anterior wall of the aortic root was in continuity with the echo from the interventricular septum. In the echocardiograms from the aortic root/left atrium the aortic root diameter (AOD) and a left atrial dimension (LAD) as outlined in Fig. 3 were measured. These measurements were made at end-systole defined as the end of the *T* wave in the simultaneously recorded electrocardiogram.

The echocardiogram from the interventricular septum/posterior left ventricular wall was obtained with the transducer in the fourth left intercostal space close to the sternal border. The echo from the anterior mitral leaflet was first identified and then the ultrasonic beam was angulated slightly in the inferior and lateral direction. The characteristic echocardiogram of

the interventricular septum and the posterior left ventricular wall (Fig. 4) was thus obtained. It was considered important to obtain the echocardiogram with the ultrasonic beam slightly inferior and lateral to the anterior mitral leaflet, but still close to the mitral valve. On the echocardiogram obtained in this way the following measurements were made left ventricular internal dimension (LVID), right ventricular dimension (RVD), the distance between the anterior chest wall and the right side of the interventricular septum (O-IVS) as outlined in Fig. 4 The width of the interventricular septum (IVS-width) was also measured. All these measurements were made at end-diastole, defined as the peak of the R wave in a simultaneously recorded electrocardiogram.

The echocardiogram from the anterior tricuspid leaflet was obtained with the transducer in the fourth left intercostal space at the sternal border and angulated 10–45° in the medial direction. If the right ventricle was dilated this echo could be obtained with the transducer in the antero-posterior direction. This echo has a pattern of movement similar to that of the echo from the anterior mitral leaflet (Fig. 2) In some infants a complete echo could be obtained, but in other infants and in all children without heart disease the echo from the anterior tricuspid leaflet was incomplete and consisted mainly of an echo during ventricular systole and with a rapid anterior opening movement at the beginning of diastole. When possible the same measurements as for the echo from the anterior mitral leaflet were made.

Material The normal material consisted of 64 infants and children (33 girls and 31 boys), without heart disease, aged from 3 days to 15 years. An attempt was made to examine 4 more children, aged 1 to 3 years, but the examination could not be completed because of the children s uncooperativeness.

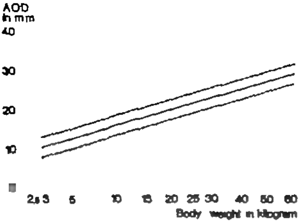
Test of reproducibility of the echocardiographic measurements On the subjects included in this part of the investigation a complete echocardio-

Table 1 *Reproducibility of the echocardiographic measurements expressed as a 95% confidence interval of the measurement or as a coefficient of variation*

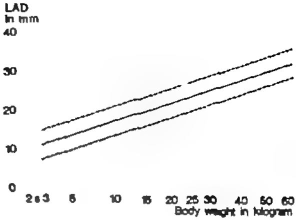
		95 confidence interval (mm)	Coefficient of variation (%)
AOD	Mean of 10 measurements	±1.2	2 5
	Mean of 5 measurements	±1 3	2 5
LAD	Mean of 10 measurements	± 6	3–7
	Mean of 5 measurements	±2.7	3–7
LVID	Mean of 10 measurements	±1.9	1–4
	Mean of 5 measurements	±2.0	2 5
O–IVS	Mean of 10 measurements	±2.8	3–5
	Mean of 5 measurements	±3.0	3–5
RVD	Mean of 10 measurements	±1 1	3–6
	Mean of 5 measurements	±1.2	3–7
AM ampl	Mean of 10 measurements	±1.5	–6
	Mean of 5 measurements	±1.9	3–7

Table 2. *Comparison between echocardiographic normal values for infants and children given by Feigenbaum (41) and those obtained in the present investigation*

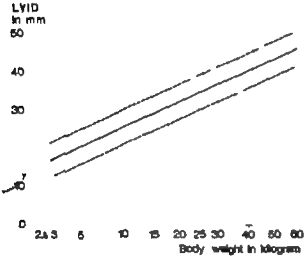
	Body weight (kg)	Range of normal values, mm: Feigenbaum (41)	Present investigation
RVD	<11	3–15	4–11
	12–22	4–15	4–11
	23–34	7 18	4–11
	35–45	7–16	4–11
	46–56	8–17	4–11
LVID	<11	13–32	12 31
	12–22	4–38	22–37
	23–34	33–45	28–42
	35–45	35–47	33–46
	46–56	37–49	37–49
IVS-width	<11	4–6	3–5
	12–22	5–7	4–6
	23–34	6–7	5–7
	35–45	7–8	5–7
	46–56	7–8	5–7
LAD	<11	7–23	7–22
	12–22	17–27	15–27
	23–34	19–28	19–30
	35–45	20–30	24–33
	46–56	21 30	26–35
AOD	<11	7–17	8–19
	12 22	13–22	14–24
	23–34	17–23	19–26
	35–45	19–27	21 29
	46–56	17 27	23–31



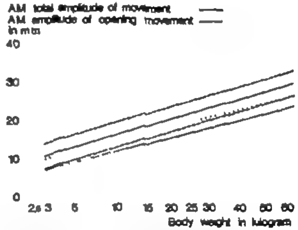
Aortic root diameter (AOD)



Left atrial dimension (LAD)



Left ventricular internal dimension (LVID)



Total amplitude of movement and amplitude of opening movement of the echo from the anterior mitral leaflet (AM).

Right ventricular dimension (RVD)
95 % prediction interval for all ages, 4.3–10.3 mm

Width of interventricular septum (IVS)

Body weight in kg	IVS-width in mm
<10	3–5
10–25	4–6
>25	5–7

Speed of movement in posterior direction of the echo from the anterior mitral leaflet during diastole

Age in years	Speed of movement in mm/sec
<1	90–130
>1	90–180

Fig. 5. Normal values of echocardiographic findings in infants and children. The nomograms are based on the linear correlation between the different echocardiographic measurements and the cube root of the body weight. The regression lines and the 95 % prediction intervals are given.

graphic examination as outlined above was performed. Enough recordings were obtained to allow 10 measurements of all data required. Eleven subjects, aged from 2 months to 16 years, were examined with echocardiography on 2 consecutive days. Of these, however, 7 were infants and children with various forms of congenital heart disease randomly selected from the patients examined with echocardiography during a short period of time.

Results. No significant difference was found between girls and boys and the results are there-

fore presented for the entire material. In the test of the reproducibility of the echocardiographic measurements a statistical analysis was made with a comparison of the results of the various measurements made on the first and the second day. This comparison was made both with the results given as a mean of 10 and as a mean of 5 measurements. The result of this comparison was expressed as a 95 % confidence interval of the measurement and is shown in Table 1. If the standard deviations used in the estimation of these confidence intervals were diveded by the actual smallest and largest measurements (mean of 10 or 5 measurements), a coefficient of variation is obtained (Table 1). As can be seen in Table 1 the coefficient of variation increased only slightly if the results were expressed as a mean of 5 measurements instead of a mean of 10 measurements. The results for the rest of this investigation were therefore expressed as means of 5 measurements.

Satisfactory echocardiographic recordings from the four regions examined could be obtained in all infants and children in whom this examination could be completed. For most of the intracardiac distances measured a linear correlation was found to the height, to the cube root of the bodyweight and to the cube root of the age of the subjects. Since the best correlation was to the cube root of the bodyweight the normal values for these distances are given as nomograms for prediction of the various distances (Fig. 5). For the right ventricular dimension, the width of the interventricular septum and the speed of movement of the echo from the anterior mitral leaflet during diastole nomograms were not constructed since these normal values are easily given without (Fig. 5). In Table 2 the normal values encountered in the present investigation are compared with the largest normal material presented covering the same age groups (41).

ECHOCARDIOGRAPHIC EXAMINATIONS OF THE AORTIC ROOT/LEFT ATRIUM (II)

Material. During a period of 18 months, an echocardiographic examination was performed on every infant and child undergoing heart catheterization and angiocardiography. On the angiocardiograms a satisfactory measurement of the aortic root diameter could be made in 166 cases and a measurement of the left atrial diameter in 91 cases. In this original material three patients had to be excluded due to unsatisfactory echocardiograms. The reasons for this were malposition of the heart (situs inversus and mediastinal tumour) in two cases and the inability to obtain any intracardiac echoes at all in one patient, presumably due to interposition of lung tissue in front of the heart secondary to severe obstructive bronchitis. The echocardiographic examination of the aortic root/left atrium as used in the present investigation is dependent upon a normally positioned aortic root. The patients with transposition of the great arteries, corrected transposition with ventricular inversion, truncus arteriosus communis and double outlet right ventricle were therefore excluded for the comparison between echocardiography and angiocardiography. After exclusion of these patients there remained 148 patients in whom a comparison between echocardiography and angiocardiography could be made with respect to the aortic root and 79 patients with respect to the left atrium.

Methods. The echocardiographic examination was made as outlined in a previous chapter. In most cases it was performed the day before the angiocardiography. The echocardiographic investigation was performed without premedication. A few nervous children, who could not be examined in this way, were studied a few hours after the angiocardiography while still under the influence of the premedication given for this examination. The aortic root diameter (AOD)

Table 3 *Diagnosis of the patients where the aortic root diameter measured by echocardiography was above the upper normal limit*

Diagnosis	Number of patients
Fallot's anomaly	13
Coarctation of the aorta	5
Ventricular septal defect	5
Valvular aortic stenosis	3
Aortic regurgitation	1
Patent ductus arteriosus	1
Dilated ascending aorta	1
Aneurysm of sinus of Valsalva	1
Anomalous origin of left coronary artery from the pulmonary artery	1
Third degree AV-block	1

and the left atrial dimension (LAD) as shown in Fig. 3 were measured and the results given as a mean of 5 measurements.

The radiological measurements were made on full size angiocardiograms. The requirements the angiocardiograms used in this study were the aortic root or left atrium should be / outlined irrespective of the site of the contrast injection. The antero-posterior diameter of the aortic root just above bulbus aortae was measured on the angiocardiogram in the lateral projection. In the angiocardiograms of the left atrium made in the lateral projection, the largest sagittal diameter was measured. The measurements were made at the end of ventricular systole.

Results The aortic root diameter measurements obtained by echocardiography (AOD) and those obtained by angiocardiography showed a close linear correlation over a very wide range of values ($r = 0.98$ $y = 1.10x - 0.48$ S.D 1.70). The angiocardiographic measurements were slightly larger than the echocardiographic measurements This discrepancy is not surprising since no correction of the magnification of the angiocardiographic measurements was made.

The left atrial dimension measured by echocardiography (LAD) and the left atrial sagittal diameter measured by angiocardiography showed a good linear correlation ($r = 0.93$ $y = 1.08x$ 7.90- S.D 2.99) The angiographic measurements were larger than the echocardiographic measurements. This is to be expected as the former represents a diameter in the antero-posterior direction whereas the latter is a dimension measured in an oblique direction. Besides this, correction for the magnification of the angiocardiographic measurements was not made.

Comments For evaluation of the application of these echocardiographic measurements for clinical use it should be of interest to know the diagnosis of the patients in whom these measurements fell outside the normal range. The echocardiographic measurements of the aortic root diameter (AOD) were therefore compared with the normal values given in Fig. 5 (95 % prediction interval). In 32 of the 148 patients (21 %) the values were above the upper normal limit. The diagnoses of these patients are given in Table 3 Four patients (3 %) had AOD-values below the lower normal limit. Three of these patients had aortic valve atresia and no echoes from the aortic leaflet could be obtained The fourth patient had a supravalvular aortic stenosis, at the level at which this measurement was made

Most of the patients with Fallot's anomaly had an enlarged aortic root diameter Only two of the patients with Fallot's anomaly had a normal AOD one examined at the age of 2 weeks and the other examined several years after a total correction. Two patients with aortic regurgitation were examined with full-size angiocardiograms, one of these had an enlarged AOD The patient with a third degree AV-block deserves some comment. He was first examined at the age of 1 day and showed a normal AOD according to both echocardiography and angiocardiography At a reexamination at the age of 5 months his AOD was definitely above the upper normal limit using echocardiography and the ascending aorta was clearly enlarged on the angiocardiogram.

As expected the three patients with aortic valve atresia had a narrow aortic root, and no echoes were obtained from the aortic leaflets. However in two neonates with an aortic valvular stenosis as part of a hypoplastic left heart

syndrome later studied (99), narrow aortic roots were found at the echocardiographic examination, but with an echo from an aortic leaflet.

When the results of the echocardiographic measurements of the left atrial dimension (LAD) were compared with the normal values given in Fig. 5 (95% prediction interval) 31 of 79 patients (39%) had values of the LAD above the upper normal limit. The diagnoses of these patients are given in Table 4. Two patients had LAD-values below the lower normal limit. One had a valvular aortic atresia and the other Fallot's anomaly. The LAD-value of the latter patient was just below the lower normal limit.

The majority of patients with LAD-values above the upper normal limit had a left to right shunt below the atrioventricular level. Only one patient with this diagnosis had a LAD-value within the normal limits. This patient had a ventricular septal defect with pulmonary hypertension at systemic level, increased pulmonary vascular resistance and only a small left to right shunt.

The patients with coarctation of the aorta and increased LAD-values either had complicating lesions or signs of congestive heart failure. Six older patients with isolated coarctation of the aorta all had LAD-values within the normal limits.

Table 4. *Diagnosis of the patients where the left atrial dimension measured by echocardiography was above the upper normal limit*

Diagnosis	Number of patients
Ventricular septal defect	15
Ventricular septal defect + coarctation of the aorta	2
Ventricular septal defect + mitral regurgitation	1
Patent ductus arteriosus	2
Coarctation of the aorta	2
Coarctation of the aorta + mitral regurgitation	2
Coarctation of the aorta + mitral stenosis	1
Mitral regurgitation	
Valvular aortic stenosis	1
Anomalous origin of left coronary artery from pulmonary artery + mitral regurgitation	1
Cardiomyopathy with mitral regurgitation	1
Myocarditis	1

The only patient with valvular aortic stenosis and increased LAD-value had a very severe aortic stenosis with signs of congestive heart failure during the first months of life. A valvotomy of the aortic valve was performed. Post-operative echocardiographic examinations showed normal LAD-values. The patient with myocarditis and an increased LAD-value showed signs of congestive heart failure.

ECHOCARDIOGRAPHIC EXAMINATION OF THE LEFT AND RIGHT VENTRICLE (III)

Material. This investigation was part of the same comparison between echocardiography and angiocardiography referred to in the previous chapter. From the material collected during 18 months, 65 infants and children had a satisfactory angiocardiogram of the left ventricle. Out of these 65 patients 5 had to be excluded, due to the failure to obtain a satisfactory echocardiogram in one case and to malposition of the heart in two cases. These patients have been referred to in the previous chapter. The remaining two excluded patients both had corrected transposition of the great arteries with ventricular inversion. In these patients it was impossible to get any echoes from the interventricular septum, presumably due to its abnormal spatial orientation in this malformation.

A satisfactory angiocardiogram of the right ventricle was obtained in 92 patients. From this material 8 patients had to be excluded. Three of them were those referred to above where either no cardiac echoes could be obtained or where the heart was abnormally placed. In the remaining 5 patients no echoes from the interventricular

Table 3 *Diagnosis of the patients where the aortic root diameter measured by echocardiography was above the upper normal limit*

Diagnosis	Number of patients
Fallot's anomaly	13
Coarctation of the aorta	5
Ventricular septal defect	5
Valvular aortic stenosis	3
Aortic regurgitation	1
Patent ductus arteriosus	1
Dilated ascending aorta	1
Aneurysm of sinus of Valsalva	1
Anomalous origin of left coronary artery from the pulmonary artery	1
Third degree AV-block	1

and the left atrial dimension (LAD) as shown in Fig. 3 were measured and the results given as a mean of 5 measurements.

The radiological measurements were made on full size angiocardiograms. The requirements of the angiocardiograms used in this study were al the aortic root or left atrium should be y outlined irrespective of the site of the contrast injection The antero-posterior diameter of the aortic root just above bulbus aortae was measured on the angiocardiogram in the lateral projection. In the angiocardiograms of the left atrium made in the lateral projection the largest sagittal diameter was measured The measurements were made at the end of ventricular systole.

Results The aortic root diameter measurements obtained by echocardiography (AOD) and those obtained by angiocardiography showed a close linear correlation over a very wide range of values ($r = 0.98$ $y = 1.10x - 0.48$ S.D 1.70). The angiocardiographic measurements were slightly larger than the echocardiographic measurements This discrepancy is not surprising since no correction of the magnification of the angiocardiographic measurements was made.

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Coarctation of the aorta	-
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Mitral regurgitation	
Valvular aortic stenosis	1
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Cardiomyopathy with mitral regurgitation	1
Myocarditis	1

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Ventricular septal defect	5
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Aortic regurgitation	1
Patent ductus arteriosus	1
Dilated ascending aorta	1
Aneurysm of sinus of Valsalva	1
Anomalous origin of left coronary artery from the pulmonary artery	1
Third degree AV-block	1

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As expected the three patients with aortic valve atresia had a narrow aortic root, and no echoes were obtained from the aortic leaflets. However in two neonates with an aortic valvular stenosis as part of a hypoplastic left heart

Table 5 *Diagnosis of patients where the left ventricular internal dimension (LVID) measured by echocardiography was above the upper normal limit*

Diagnosis	Number of patients
Ventricular septal defect	
Patent ductus arteriosus	1
Ventricular septal defect patent ductus arteriosus	1
Aortic regurgitation	2
Mitral regurgitation	
Anomalous origin of left coronary artery from the pulmonary artery	1
Fibroelastosis	1

Table 6 *Diagnosis of patients where the right ventricular dimension (RVD) measured by echocardiography was above the upper normal limit*

Diagnosis	Number of patients
Atrial septal defect	13
Atrial septal defect entricular septal defect	
Ventricular septal defect	7
Ventricular septal defect with pulmonary hypertension	1
Ventricular septal defect – tricuspid regurgitation	1
Total anomalous pulmonary enous return	3
Aortic valvular atresia	2
Pulmonary lvular stenosis	10
Fallot' anomaly	5
Fallot anomaly after total correction	3
Fallot anomaly after total correction with pulmonary alvular regurgitation	
Primary pulmonary hypertension	1
Truncus arteriosus communis	
Transposition of the great arteries	1
Double outlet right entricle	1
Coarctation of the aorta	1
Third degree AV-block	1
Myocarditis	1

patients with aortic valve atresia but the angiocardiograms of these patients were not of a high enough quality to warrant inclusion in this material.

The patients with   entricular septal defects and/or patent ductus arteriosus with large LVID-values all had very large *left to right* shunts. Four patients with ventricular septal defect or patent ductus arteriosus had normal LVID-values. Two of these patients had only a small left to right shunt but the other two had a large left to right shunt. The patients with aortic or mitral regurgitation and large LVID-values all had severe regurgitation. One patient with aortic regurgitation and three with mitral regurgitation showed normal LVID- values. One of these patients had a moderate mitral regurgitation while the others had a *slight regurgitation* The patients with an anomalous origin of the left coronary artery and fibroelastosis both showed signs of congestive heart failure.

The RVD-values measured by echocardiography were found to be above the upper normal limit (upper limit of 95% prediction interval) in a large number of patients (57 out of 84 patients. 68) The diagnoses of these patients are presented in Table 6. RVD-values below the lower normal limit were not encountered in any patient. Only one patient with atrial septal defect was found to have a normal value of the right ventricular dimension by echocardiography This patient had just a minimal left to right shunt. An enlargement of the right ventricle in one patient with coarctation of the aorta and in one patient with myocarditis was presumably due to severe congestive heart failure. Some of the patients with pulmonary valvular stenosis, Fallot s anomaly and ventricular septal defects had large RVD-values and some had normal RVD-values.

ECHOCARDIOGRAPHIC EXAMINATION OF THE MITRAL VALVE REGION (IV V)

Material For the echocardiographic study of the mitral valve region infants and children with *malformations affecting the mitral val e region* and verified by operation or autopsy were chosen Patients with congenital mitral stenosis which was not part of a hypoplastic left heart complex

constituted one group studied. The mitral stenosis was considered as congenital because it was detected very early (during the first year of life) and besides none of the patients had a rheumatic fever in their past history This part of the study included all 7 patients with congenital mitral stenosis seen during a period of 5 years and on whom an echocardiographic examination had been performed. All patients were examined with heart catheterization and angiocardiography and the diagnosis was verified at operation in five of the patients and at autopsy in the remaining two patients. Five of the patients also had a postductal coarctation of the aorta and one patient had a patent ductus arteriosus with a large left to right shunt. The remaining patient had a more complex malformation with a large ventricular septal defect, a patent ductus arteriosus and a preductal coarctation of the aorta The degree of the mitral stenosis was based on the findings at operation or autopsy

The material was divided into two groups, severe mitral stenosis with obvious hemodyna consequences and slight mitral stenosis presumably without hemodynamic consequences. The mobility of the mitral valve was also studied at operation or autopsy The operation consisted of a valvotomy of the mitral valve in four patients. Surgical procedures aimed at correction of other concomitant cardiovascular malformations were carried out at the same time. In one of the patients a valvotomy could not be made and the mitral valve had to be replaced with a prothesis. The four patients who underwent a mitral valvotomy had been checked by postoperative investigations, including heart catheterization and angiocardiography in three of them.

The patients in the other part of this study consisted of young infants with malformations in the mitral valve region verified at autopsy These patients were investigated during a period of three years and included all patients with that diagnosis and on whom an echocardiographic investigation had been performed Three patients had mitral atresia. Two of these were combined with a single ventricle and the third with a ventricular septal defect. Four patients had aortic valvular atresia combined with a moderate or severe mitral stenosis. The left ventricle was severely hypoplastic in these patients. Five patients had mitral stenoses of varying degrees combined with aortic valvular stenosis. The degree of hypoplasia of the left ventricle was moderate in one of the patients and severe in two The remaining two patients had a left ventricle of normal size. One of them had a severe endocardial fibroelastosis and the other a complex malformation consisting of a supra valvular ring in the left atrium, a parachute deformity of the mitral valve and a coarctation of the aorta Two more patients were included in this study although they did not have a malformation directly involving the mitral valve One was a patient with a membrane dividing the left atrium into two parts (cor triatriatum) and the other a patient with a severe isolated aortic valvular stenosis without hypoplasia of the left ventricle.

Methods The echocardiographic examination was performed as described previously Great efforts were made to obtain registrations with an echo from the anterior mitral leaflet with as large an amplitude of movement as possible

Results An echocardiogram from the anterior mitral leaflet could be obtained in all the 7 patients with congenital mitral stenosis. The total amplitude of movement and the amplitude of the opening movement at the beginning of diastole were within normal limits, albeit in the lower normal range in five of these patients. At operation the mobility of the mitral valve was found to be satisfactory in four of these patients and a mitral valvotomy was performed in three of them. In the fifth patient the mobility of the anterior mitral leaflet was found to be satisfactory at autopsy In two patients the total amplitude of movement and the amplitude of the opening movement at the beginning of diastole were below the lower normal limit. One of these patients died and autopsy revealed a severely deformed mitral valve. It was considered likely that the mobility of the mitral valve had been restricted On operating the other

child it was found that the mobility of the mitral valve was restricted and a valvotomy was not considered possible. A replacement of the valve was therefore performed.

The diastolic closure rate of the echo from the anterior mitral leaflet (*E–F* in Fig. 2) could be measured in all the 7 older infants and children with mitral stenosis. The speed of movement was found to be much slower than the lower normal limit (90 mm/sec) in all of them. Two of the patients had a speed of movement between 30 and 40 mm/sec. At autopsy or operation the degree of mitral stenosis was judged to be slight in both these patients. The other 5 patients had a speed of movement below 25 mm/sec. At operation or autopsy the degree of mitral stenosis was judged to be severe in all 5 patients. Echocardiographic examination of the anterior mitral leaflet was performed after mitral valvotomy in three patients and after an exploration of the mitral valve in one patient. The values of the diastolic closure rate had increased in all and were now in or above the range (30–40 mm/sec) supposed to indicate a slight mitral stenosis. At follow-up investigations 1–5½ years after operation the values were not significantly altered. These findings were assumed to indicate satisfactory results of the valvotomy. Post-operative clinical investigations confirmed that the result of the valvotomy was satisfactory in all patients. Postoperative cardiac catheterization was performed in all patients except one and showed a reduction in the pressure in the pulmonary artery and the pulmonary capillary wedge position, indicating a satisfactory result of the operation.

In the three patients with mitral atresia the echo from the mitral region moved in the anterior direction during ventricular systole but in the posterior direction during ventricular diastole and an opening (anterior) movement in diastole was thus not seen. It is believed that the echo obtained in these cases originated from the atretic mitral valve region.

In the remaining young infants the echo from the mitral valve region showed a rapid anterior opening movement at the beginning of diastole identifying the echogiving structure as the anterior mitral leaflet. In all these infants the heart rate was too rapid to allow measurement of the speed of movement in the posterior direction during diastole before atrial systole (*E–F* in Fig. 2). In all the patients with mitral stenosis combined with aortic valvular atresia or aortic valvular stenosis the pattern of movement of the echo from the anterior mitral leaflet was abnormal during diastole. From the most anterior position at the early part of diastole the echo moved slowly in the posterior direction during the entire diastole, ending with a more rapid closing movement at the end of diastole. Normally the echo from the anterior mitral leaflet moves more rapidly in the posterior direction immediately after the most anterior opening position has been reached (point *E* in Fig. 2). The deviation from the normal in these cases could be seen by inspection but could not be quantified in a reliable manner. The patients with mitral stenosis combined with aortic valvular atresia or stenosis could, however, be separated into two groups based on the amplitude of the opening movement at the beginning of diastole. Six of the patients had a very low amplitude of opening movement of 1 to 3 mm compared to the normal 7–9 mm. This group of patients was anatomically characterized by a very tight mitral stenoses combined with a moderate or severe degree of hypoplasia of the left ventricle, or alternatively by a slight or moderate mitral stenosis combined with a severe degree of hypoplasia of the left ventricle. In both circumstances it seems likely that the hemodynamic function of the left ventricle was extremely limited. The other group of three patients had an amplitude of opening movement at the beginning of diastole of 5–6 mm, which is only slightly below normal. This group was anatomically characterized by a slight mitral stenosis combined with a moderate degree of hypoplasia of the left ventricle, or alternatively by a moderate degree of mitral stenosis combined with a normal sized left ventricle.

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In the young infants with mitral stenosis combined with aortic valvular atresia or aortic valvular stenosis it was only possible to demonstrate echoes from the posterior mitral leaflet in two patients. In both, the echo from the posterior mitral leaflet moved in a normal way (Fig. 7) These two patients had a slight mitral stenosis combined with an aortic valvular stenosis. The degree of hypoplasia of the left ventricle was moderate in the one and severe in the other

ECHOCARDIOGRAPHIC EXAMINATION OF THE TRICUSPID VALVE REGION (VI)

Material During a five year period all patients with Ebstein's anomaly of the tricuspid valve were examined by echocardiography and included in this study The age of these ten patients ranged between 4 days and 20 years at the first echocardiographic examination. In addition, nine other patients with this anomaly from two other hospitals were examined by the author on one occasion The ages of these patients were between 1½ and 40 years. The diagnosis was confirmed by heart catheterization and angiocardiography in all cases except one The diagnosis in this patient was based on typical physical findings, and typical findings on the electrocardiogram and at roentgen examination of the heart. Associated cardiovascular malformations were not encountered except for an atrial septal defect. One of the patients died at the age of 6 months and the diagnosis was confirmed at autopsy

For comparison purposes some other patients with echocardiography of the tricuspid valve were included. This group comprised patients with atrial septal defects, total anomalous pulmonary venous return, complete right bundle branch block, and pulmonary hypertension One patient with congenital tricuspid stenosis was also included

Methods The echocardiographic examinations were performed as described previously In the echocardiogram from the anterior tricuspid leaflet the amplitude of opening movement at the beginning of diastole was measured. Whenever possible the speed of movement in the posterior direction during diastole was measured in a similar way to the anterior mitral leaflet measurements The time intervals from the Q wave in a simultaneously recorded electrocardiogram to the time of opening and closure of the tricuspid and mitral valves were measured. In twelve patients with Ebstein's anomaly of the tricuspid valve echoes from the anterior tricuspid and anterior mitral leaflet could be registered simultaneously On these recordings the time interval between mitral and tricuspid closure and between the mitral and tricuspid opening were measured.

Results An echo supposed to come from the anterior tricuspid leaflet was obtained in all the patients with Ebstein's anomaly In order to verify the origin of this echo the contrast echo method described by Gramiak et al (64) was used in one patient. During heart catheterization indo-cyanine green was injected into the right atrium while an echocardiogram was registered. Indo-cyanine green injected in this way produces dense echoes and thereby allows identification of intracardiac echoes. By this investigation the echogiving structure was identified as the anterior tricuspid leaflet.

The echo from the anterior tricuspid leaflet in patients with Ebstein's anomaly differed from that obtained from patients with a normal tricuspid valve with respect to its movement during diastole. A normal rapid opening movement at the beginning of diastole occurred but during the remaining part of diastole the echo moved only slowly in the posterior direction. The speed of this posterior movement could be measured in 10 patients and was below 35 mm/sec. Normal values for this speed of movement and the amplitude of movement are not available since it is difficult to obtain a

complete echo from the anterior tricuspid leaflet in patients without heart disease. When measurable in patients with other malformations the speed of movement of anterior tricuspid leaflet was above 75 mm/sec. Since no normal values for the amplitude of movement of the anterior tricuspid leaflet are obtainable it is difficult to assess the mobility of the anterior tricuspid leaflet in the patients with Ebstein s anomaly It could be approximately evaluated by comparison with the amplitude of movement of the anterior *mitral* leaflet in the same patient or with the amplitude of movement of the echo from the anterior tricuspid leaflet in patients with other cardiovascular malformations not directly involving the tricuspid valve. Using this crude comparison it was suspected that the amplitude of movement of the echo from the anterior tricuspid leaflet was increased in 5 patients with Ebstein s anomaly decreased in two and presumably normal in the majority of the patients. In two of the patients the amplitude of movement of the echo from the anterior tricuspid leaflet s double or almost double the amplitude of vement of echo from the anterior mitral eaflet (normal for weight) indicating a highly increased mobility of the anterior tricuspid leaflet.

At the end of diastole the echo from the anterior tricuspid leaflet was in an abnormally anterior position in all the patients with Ebstein s anomaly From this position the echo moved rapidly to a fully closed position. The fully closed position was, however reached later than normal (0 10–0.21 sec after the Q-wave in the simultaneously recorded electrocardiogram).

On comparing the time of mitral and tricuspid opening in the patients with Ebstein s anomaly it was found that mitral opening was simultaneous with tricuspid opening in six patients but occurred before tricuspid opening in 13 patients. A normal relation between mitral opening and tricuspid opening was thus apparent in many of the patients and only a few showed a delayed tricuspid opening. The tricuspid closure did, however occur much later (0 06 sec or more) than the mitral closure in all patients with Ebstein s anomaly of the tricuspid valve This asynchrony may possibly be explained by the right bundle branch block seen in patients with Ebstein s anomaly A comparison between the time interval between the mitral and tricuspid closure related to the duration of the QRS-complex was therefore made in patients with Ebstein s anomaly and in patients with various other conditions, including some patients with complete right bundle branch block. It was then found that the asynchrony between the mitral and tricuspid closure for any given QRS-duration was greater for the patients with Ebstein s anomaly than for any of the other patients studied.

In the patient with congenital tricuspid stenosis a deformation of the thoracic cage made the echocardiographic examination difficult to perform. An echo supposed to originate from the anterior tricuspid leaflet could be obtained having only a minimal opening movement at diastole. Details about the further movement during diastole could not be obtained and the investigation is therefore not conclusive.

Comments. After the publication of these experiences of echocardiography in the diagnosis of Ebstein s anomaly two more newborn infants with this anomaly have been investigated (99). One of these patients was examined at the age of one day She had moderate cyanosis. At echocardiography echoes from the anterior tricuspid leaflet and the anterior mitral leaflet were obtained simultaneously The echo from the anterior tricuspid leaflet had a large amplitude of movement (6 mm larger than the amplitude of movement of the echo from the anterior mitral leaflet). The tricuspid closure occurred late, 0 14 sec. after the mitral valve closure. The diagnosis was confirmed by heart catheterization and angiocardiography The condition of this patient has later improved and she is now almost symptomfree The other newborn infant was examined at the age of 3 days. She had severe cyanosis. At echocardiography the amplitude of movement of the echo from anterior tricuspid leaflet was unusually small (4 mm less than the corresponding amplitude of movement

of the echo from the anterior mitral leaflet recorded simultaneously). The closure of the tricuspid valve occurred after (0.11 sec) the mitral valve closure. This patient died and an autopsy revealed a severely deformed tricuspid valve typical of Ebstein's anomaly but even the anterior tricuspid leaflet was found to be underdeveloped.

Recently it has been reported in a few adult patients with Ebstein's anomaly of the tricuspid valve that the speed of movement in the posterior direction during diastole can be normal (69, 90, 150). Recent own experiences and those of other authors have led to a modification of the conclusion about echocardiography in the diagnosis of Ebstein's anomaly of the tricuspid valve (98). In Ebstein's anomaly of the tricuspid valve abnormal echocardiographic findings from the tricuspid valve region have been found in all reported cases. The constant and most specific finding has been a delayed tricuspid valve closure compared with mitral valve closure. The amplitude of movement of the anterior tricuspid valve is often increased, but may be normal or even reduced. The speed of movement of the anterior tricuspid leaflet at diastole is often reduced but may be normal.

GENERAL DISCUSSION

Identification of intracardiac echoes

In applying echocardiography a basic requirement must be the identification of the sources of the intracardiac echoes. This was discussed in detail in a review article by Edler (29) and summarized in the following words: "In order to identify the heart structures from which a given echo emanates, it is necessary: (1) to analyze the tracing's movement pattern and correlate this with simultaneously recorded ECGs and intracardiac pressure recordings; (2) to determine the echo's localization within the heart, that is to say, to determine the distance between the transducer on the precordium and the echo source; and (3) to consider the heart in situ." The last point has been documented by experiments on the isolated heart (33) and by insertion of needles along the ultrasonic path on cadavers (27). Complementing these experimental and indirect proofs of the nature of the echogiving structures within the heart a contrast echo method was introduced (64) providing in-vivo confirmation of the origin of the intracardiac echoes. It was demonstrated that the rapid injection of various substances (especially indo-cyanine green) into a heart chamber or a vessel produced dense ultrasound echoes, probably arising from the formation of microbubbles. This phenomenon was used for the identification of different intracardiac echoes (64) and has later been used by several investigators (44, 86).

Most of the echoes studied in the present investigation have been adequately identified previously. However, due to the altered anatomy in the tricuspid valve region in Ebstein's anomaly it was found necessary in the present study to identify the echogiving structure by the contrast echo method. For the various echoes from the mitral valve region in young infants (IV) the identification was based on the following parameters: (1) the direction and depth at which the echo was obtained, (2) the relation to other ultrasound echoes of known origin, (3) a characteristic movement of the echo in relation to the electrocardiogram and (4) relation of echocardiographic findings to anatomic findings at autopsy or findings at angiocardiography. The use of the contrast-echo method in these cases would have been of value but was not possible at the time.

Reproducibility of echocardiographic measurements

Another basic requirement of the echocardiographic examination is the reproducibility of

echocardiographic measurements. Despite the rapidly increasing number of reports about echocardiography in infants and children no information seems to be available about the reproducibility of the echocardiographic measurements in these age groups. This information is sparse even concerning adults but yet exist concerning measurements of left ventricular dimensions and volumes (119) and a study of the mitral valve (67) The basis for reproducible results is in turn a proper standardization of the technique. For the measurements of the aortic root diameter and the left atrial dimension the importance of standardization of the technique has not been found to be the subject of any discussion previously For the measurement of the left ventricular internal dimension several authors have, however discussed the standardization (40, 52, 104 114 119 120 124)

The results here reported about the reproducibility of the echocardiographic measurements agree quite well with those few studies concerning this subject in adults (67 119).

The *conclusion* of this part of the study is that reproducibility of the echocardiographic measurements seems to be quite adequate for permitting meaningful comparisons between different patients and between different investigations in the same patient. The question about reproducibility should also apply to a comparison between examinations made by different persons on the same patient. An answer to this question can unfortunately not be given in the present investigation since all the echocardiographic examinations were made by one person. In adults it has however been shown (119) that the difference in results between two observers examining one echocardiogram is smaller than the difference between two different examinations on the same patient made by one examiner

Echocardiographic investigations of infants and children without heart disease

The different normal values given in the present investigation agree as a whole quite well with those published previously on infants and children (106, 151 163). More extensive normal values for different echocardiographic distances in infants and children have quite recently been published (41) In general they compare favourably with those presented here (Table 2). The main exception is the values of the right ventricular dimension (RVD) in which the upper normal limits given in the present investigation are 4–6 mm lower than those given by Feigenbaum (41). The reason for this difference is presumably that the anterior border of the echofree space representing the right ventricle (Fig. 4) was often difficult to delineate distinctly in the present material. The value for the RVD was therefore taken as the largest measurement obtained It seems likely that focused transducers were used in Feigenbaum s investigation (41). A better resolution can presumably then be obtained with resulting clearer delineation of the anterior border in question. This type of focused transducer was not available for the present investigation

For the neonatal period normal values for different echocardiographic measurements have also recently been published (70, 145) The mean values in the report by Solinger et al. (145) agree well with those presented here although the range is narrower The values for the right ventricular dimension (RVD) reported by Solinger et al. (145) cannot be compared with those presented here or in other studies (41 70, 106, 151) since quite different technique was used The narrower range of normal values reported by Solinger et al. (145) in the neonatal period probably arises from the use of a transducer with a much higher frequency (5–10 MHz compared with 2.25 MHz in the present investigation). This high frequency transducer which can presumably increase the resolution when examining neonates, was not available for the present investigation.

Investigation of the aortic root/left atrium

The echocardiographic investigation of the aortic root/left atrium as presented here is based on a normal position of the aortic root. The identification of the latter is thus of great importance.

Echoes from the aortic root were obtained with the transducer in the third or second left intercostal space and directed in the medial-cranial direction. An echocardiogram as presented in Fig. 3 was then obtained. Those patients in whom this type of echocardiogram was not found require further comments. In truncus arteriosus communis an echocardiogram very similar to that from an aortic root was found with the transducer in the second left intercostal space and directed in the medial or medial-cranial direction. The difference from a normal aortic root echocardiogram was that no echofree space was seen anterior to the root of the vessel. It has been shown that the echo-free space normally seen anterior to the aortic root is the outflow tract of the right ventricle (64). It could be expected that no part of the right ventricle would be found anterior to the truncus arteriosus communis. It is believed that this echocardiographic finding can contribute to the diagnosis of truncus arteriosus communis.

The identification of the outflow vessels by echocardiography in transposition of the great arteries has received interest recently (20, 58, 146). It is based on the echocardiographic identification of two outflow vessels (parallel echoes with the echo from a leaflet inbetween). According to one report (58) the echoes from the *anterior* outflow vessel were found with the transducer in the third left intercostal space angulated in the medial-cranial direction and the echoes from the *posterior* vessel (the pulmonary artery) *with the transducer at the same place* but directed in the lateral direction. According to another report (20) echoes from the two outflow vessels could be obtained simultaneously. In the present investigation echoes from an outflow vessel in the patients with transposition of the great arteries could only be obtained in two out of 6 patients. In these patients the echoes from an outflow vessel were obtained with the transducer in the third left intercostal space at *the sternal border and directed in the lateral* direction. This is quite different from the patient with a normally placed aorta and it can be assumed that these echoes originated from the pulmonary artery. In the remaining patients with transposition of the great arteries no reliable echoes from an outflow vessel were obtained. Echocardiographic identification of the outflow vessels in transposition of the great arteries was accomplished in most patients in the materials reported previously (20, 58, 146). It is possible that the use of other transducers (focused transducers or transducers of higher frequency for the neonates) can improve the possibility of identifying the outflow vessels. In corrected transposition of the great arteries with ventricular inversion no reliable echoes from an outflow vessel were found in the present material.

Another important aspect of the echocardiogram from the normally placed aortic root is that the posterior border of the aortic root is in continuity with the anterior mitral leaflet (8). This can be shown echocardiographically by tilting the transducer from recording echoes from the aortic root towards the position where an echo can be obtained from the anterior mitral leaflet. Deviations from this normal continuity are seen in patients with double outlet of the right ventricle (8) and were observed in the only patient with this malformation encountered in the present material.

To summarize this discussion it seems to be possible to identify a normally placed aortic root by echocardiography. If normal aortic root echoes are not found in the usual manner a malposition of the aorta may be suspected. A *further detailed echocardiographic examination* of the region of the outflow vessels of the heart may reveal the nature of the malformation.

If the echocardiographic examination of the aortic root is evaluated as an isolated diagnostic investigation the most useful information is found in patients with the malformations commonly referred to as the hypoplastic left heart syndrome, especially those with aortic valve atresia. The demonstration of a clearly reduced aortic root diameter in a neonate indicates an aortic valve atresia or a hypoplastic left heart with an aortic valvular stenosis. The demonstration of aortic leaflet echoes rules out aortic

valve atresia. In the majority of patients, information about the aortic root diameter must be considered together with clinical, electrocardiographical, radiological and other echocardiographical data and can thereby be of importance in the diagnostic work.

The echocardiographic estimation of left atrial size is based on the relation of the left atrium to a normally positioned aortic root. The correlation of the left atrial dimension measured by echocardiography to the left atrial sagital diameter measured by angiocardiography is fairly good and agrees well with the few reported similar investigations (77, 78). It has previously been shown that other noninvasive methods of estimating left atrial size, plain chest roentgenography and electrocardiography have obvious limitations (78, 94). With the fairly good correlation between the echocardiographic and angiocardiographic left atrial dimensions it seems justified to assume that echocardiography can provide more information about left atrial size plain chest roentgenography and electro-

The information about the size of the left atrium gained by the echocardiographic investigation shall of course, be used together with diagnostic information obtained by other means (clinical examination, electrocardiography, plain chest roentgenogram). Values of left atrial size below the lower normal limit can be expected to be found in some of the patients with a hypoplastic left heart and in patients with total anomalous pulmonary venous return (II). Echocardiographic signs of an increased left atrial size have been found mainly in patients with left-to-right shunt below the atrio-ventricular level and in patients with mitral regurgitation. In the follow-up of patients with these malformations echocardiography can be particularly useful since the method is non-invasive and easy to repeat.

In a recent report it was shown there was a linear correlation (r = 0.87) between the left atrial dimension measured by echocardiography and volume of left to right shunt in patients with isolated ventricular septal defects (7).

To summarize this part of the investigation the following *conclusions* can be drawn: (1) if an echocardiogram as shown in Fig. 3 is obtained with the transducer in the third or second left intercostal space and angulated in the medial or medial-cranial direction, it is justified to assume *that this represents a normally positioned aortic* root, provided that the posterior border of this outflow vessel is in continuity with the anterior mitral leaflet. (2) the aortic root diameter measured on this echocardiogram will show good agreement with the aortic root diameter measured by angiocardiography. (3) the echo-free space posterior to the aortic root represents the left atrium and the left atrial dimension measured on this echocardiogram shows a fairly good correlation to a left atrial sagittal diameter measured by angiocardiography.

Investigation of the left and right ventricle

The echocardiographic distance measurements used for the estimation of left and right ventricular size are based on the identification of the echoes from the posterior left ventricular wall, the echoes from the interventricular septum and the echo from the anterior wall of the right ventricle. The echoes from the posterior wall of the left ventricle are in general easy to obtain. It is however important that echoes are registered from the boundary between lung tissue and the pericardium/epicardium as well as from the endocardial surface of the left ventricle. Echoes from the interventricular septum could not be found in patients with a single ventricle. This is in agreement with the findings in a previous report (10). Septal echoes could neither be found in corrected transposition of the great arteries with ventricular inversion. The reason for this is presumably the abnormal spatial orientation of the interventricular septum in this malformation. Distinct echoes from the anterior wall of the right ventricle were sometimes difficult to obtain. This can presumably be improved by the use of other types of transducers (41, 60, 145). The importance of standardization of the investigation has already been emphasised.

In echocardiography the left ventricular internal dimension is only measured in one plane. Since this dimension showed a fairly good positive correlation to the long axis of the left ventricle measured on the angiocardiogram it was considered an acceptable assumption that it could be used as a semi-quantitative estimation of left ventricular size. A calculation of the left ventricular volume based on the measurement of only one dimension relies upon the assumption that the shape of the left ventricle is approximately the same in all patients. It has been shown that this is not true for the dilated left ventricle which has a more spherical shape than the normal left ventricle (121). Consequently actual volume estimation by echocardiography was not made.

The information about left ventricular size gained by the echocardiographic examination should be used in conjunction with other diagnostic data. More pronounced deviations from the normal have been found in the patients with a hypoplastic left ventricle and can then give more diagnostic information. A left ventricular internal dimension below the lower normal border was found in all the patients examined, in whom autopsy revealed a hypoplastic left ventricle (99). These findings agree with those reported previously (10, 106). These patients were not included in the comparison between echocardiography and angiocardiography because satisfactory angiocardiographic measurements could not be made.

With regard to the right ventricle the echocardiographic examination could distinguish between a right ventricle of normal size and an enlarged right ventricle in a comparison with angiocardiography. It is also reasonable to assume that the right ventricular dimension as measured by echocardiography will increase with increasing dilatation of the right ventricle. It has not been found possible to obtain more quantitative information about right ventricular size by echocardiography. This is in agreement with previous reports both on adults (19) and on infants and children (108, 151) although no comparison with angiocardiography was made by these authors. It has also been demonstrated that a hypoplastic right ventricle can be demonstrated by echocardiography (10, 106). This malformation was not encountered during the present investigation.

In the study of the right ventricle much attention has been paid to the pattern of movement of the echoes from the interventricular septum (19, 102, 108, 151). Normally the septum moves towards the posterior left ventricular wall during ventricular systole. The abnormal movement consists of a movement of the interventricular septum during systole parallel to the movement of the posterior left ventricular wall (type A), or hardly any movement at all (type B) during systole (19). It has been demonstrated by several investigations that this abnormal movement is seen in patients with volume overload of the right ventricle (19, 86, 102, 108, 151) but not in other patients. A few exceptions have been found, some patients with very small left-right shunts at the atrial level (102), some patients operated with closure of the atrial septal defect without residual shunt (19, 86, 102) and some patients with left-right atrial shunts combined with left ventricular volume overload (102). The change from a normal to an abnormal septal movement with the production of an atrial left-right shunt has also been demonstrated experimentally (86). In the present investigation an abnormal movement was found in most patients with volume overload of the right ventricle. The exceptions were one patient with a very small left-right shunt at the atrial level and one patient with Ebstein's anomaly of the tricuspid valve (despite the fact that this patient had a tricuspid regurgitation). The demonstration of an abnormal septal movement seems to be a valuable sign indicating a right ventricle with volume overload, though the reliability of this sign has recently been questioned (71).

The *conclusion* of this part of the investigation is that the echocardiographic distance measurements as described here provides semi-quantitative information about the size of the left and right ventricles.

Investigation of the mitral valve region

In the echocardiographic diagnosis of mitral stenosis the most important finding seems to be a severely reduced speed of movement of the echo from the anterior mitral leaflet during diastole. This can only be measured if the part of diastole before atrial systole is long enough to permit a reliable measurement. If the heart rate is too rapid (more than about 120/min) this speed of movement cannot be measured. In older infants and all children with congenital mitral stenosis this measurement could be made. The possibility of diagnosing mitral stenosis by echocardiography and also the possibility of separating a mild mitral stenosis from the more severe forms agree well with experiences from studies of adults with acquired mitral stenosis (30, 36, 67 68 82, 85, 137 169). In the present material the mitral stenosis was combined with other cardiovascular malformations but this does not seem to have affected the echocardiographic findings from the mitral valve region.

e findings after valvotomy of the mitral valve are also in agreement with those in adults with acquired mitral stenosis (30 36 67 82). The total amplitude of movement of the echo from the anterior mitral leaflet was found to be of value in evaluating the mobility of the valve just as has been found in adults (67). This can be of value in deciding whether to carry out a valvotomy or replace the mitral valve

In some patients with severe obstruction to left ventricular outflow without mitral stenosis the echocardiogram from the anterior mitral leaflet has shown a moderate reduction in the speed of movement during diastole The reason for this has been assumed to be a slow filling of the left ventricle due to reduced compliance of the left ventricle (25, 41 100 166). In infancy and childhood this has been observed in some patients with hypertrophic obstructive cardiomyopathy (97) and some with severe valvular aortic stenosis or coarctation of the aorta with signs of congestive heart failure (99). The speed of movement of the echo from the anterior mitral leaflet during diastole in the latter group has not been found to be less than about 40 mm/sec (99). If this is compared with the corresponding value of less than 25 mm/sec. in patients with *severe* mitral stenosis the difference is such that it can be used in the differential diagnosis between these two groups. A reduced speed of movement of the echo from the anterior mitral leaflet during diastole has also been reported in patients with severe right ventricular pressure overload in adults (57 105). This has been attributed to a reduced rate of left ventricular diastolic filling in these patients. A similar observation has so far not been reported in infants or children.

A study of the movement of the echo from the *posterior* mitral leaflet has been suggested for solving this problem of differential diagnosis (25) Normally the echo from the posterior mitral leaflet has a movement during diastole opposite to that of the anterior mitral leaflet. In adults with acquired mitral stenosis it has been found that the echo from the posterior mitral leaflet has a movement parallel to that of the anterior mitral leaflet during diastole (25). In patients with a reduced speed of movement of the echo from the anterior mitral leaflet during diastole with a normal mitral valve the posterior mitral leaflet has moved in a normal way (25) In the patients in the present material with severe congenital mitral stenosis the echo from the posterior mitral leaflet moved abnormally in some of the patients, but normally in others. The reason for this is presumably different kinds of malformations of the mitral valve since none of the patients had a past history of rheumatic endocarditis or showed signs of such a lesion at autopsy or operation. The finding of a normal movement of the echo from the posterior mitral leaflet in an infant or a child can thus not exclude the diagnosis of severe congenital mitral stenosis. An abnormal movement of the echo from this leaflet as described above has, however only been found in patients with mitral stenosis.

In the group of neonates and young infants characteristic echocardiographic findings from the mitral valve region have been demonstrated in mitral atresia and cor triatriatum. In these

two groups it is likely that the echocardiographic examination can constitute an important part of the diagnostic investigation.

In the relatively large group of patients with a hypoplastic left ventricle where a combination of mitral stenosis with aortic valvular stenosis or atresia is common, the echocardiographic findings from the mitral valve region were abnormal. In these patients the heart rate is usually too rapid to allow a valid measurement of the speed of movement of the echo from the anterior mitral leaflet during diastole. The abnormal movement during diastole could then only be demonstrated but not quantified. A measurement of the amplitude of movement of the echo from the anterior mitral leaflet could however be made and was of diagnostic value. Apart from mitral atresia and cor triatriatum the abnormal echocardiographic findings from the mitral valve region in this age group allowed a separation into the following three groups (1) a very tight mitral stenosis combined with a moderate or severe degree of hypoplasia of the left ventricle, or alternatively a slight or moderate degree of mitral stenosis combined with a severe degree of hypoplasia of the left ventricle (the hemodynamic function of the left ventricle presumably very limited)· (2) a slight mitral stenosis combined with a moderate degree of hypoplasia of the left ventricle or alternatively a moderate degree of mitral stenosis combined with a normal-sized left ventricle (3) a slight mitral stenosis or a severe degree of obstruction to left ventricular outflow (aortic valvular stenosis or coarctation of the aorta) combined with a normal-sized left ventricle In the neonates or young infants with mitral stenosis an echo from the *posterior* mitral leaflet could only be found in two patients and the pattern of movement of this echo was normal in both.

The *conclusion* of this part of the study is that in older infants and children a diagnosis of mitral stenosis can be made by echocardiography and, furthermore patients with severe mitral stenosis can be distinguished from those with slight stenosis. The echocardiographic examination can also be used to evaluate the results of mitral valvotomy In neonates and young infants a diagnosis of mitral atresia and cor triatriatum can probably be made by echocardiography In the group of patients with mitral stenosis and varying degree of hypoplasia of the left ventricle the echocardiographic findings can give additional diagnostic information about the functional state of the mitral valve and the left ventricle.

Investigation of the tricuspid valve region

This part of the study has been concentrated to an investigation of patients with Ebstein's anomaly of the tricuspid valve. The echocardiogram from the anterior tricuspid leaflet has often been obtained with the transducer more to the left on the precordium than usual. Echoes from the other tricuspid leaflets have not been observed.

In several of the patients the amplitude of movement of the echo from the anterior *tricuspid* leaflet has been found to be much greater than that from the anterior *mitral* leaflet. In some patients the amplitude has been the same while in a few a smaller amplitude of movement of the echo from the tricuspid leaflet has been found. A comparison with normal values is desirable but these are not available since a complete echo from the anterior tricuspid leaflet is difficult to obtain in patients without heart disease. It can be assumed that the amplitude of movement is a good measurement of the mobility of the anterior tricuspid leaflet. It is not surprising that a large amplitude of movement is often found since the anterior tricuspid leaflet is usually larger than normal in these patients (116). In some patients with Ebstein's anomaly the anterior tricuspid leaflet can be underdeveloped (116). This was exemplified in a patient with Ebstein's anomaly with severe symptoms seen recently (99). The patient died The entire tricuspid valve apparatus was severely underdeveloped. This patient showed the smallest amplitude of movement of the echo from the anterior tricuspid leaflet of all the patients with Ebstein's anomaly studied.

In most patients with Ebstein's anomaly the

pattern of movement of the echo from the anterior tricuspid leaflet is abnormal during diastole The observed abnormality is a slow posterior movement during diastole. In a few adult patients a normal speed of movement has been found however (69 90 150) The reduced speed of movement might indicate a stenosed tricuspid valve but such an interpretation seems unlikely since no signs of tricuspid stenosis could be found at heart catheterization or angiocardiography in the present material The reason for this reduced speed of movement in diastole is presumably a reduced tricuspid valve flow The few patients with a normal movement of the echo from the anterior tricuspid leaflet during diastole have been adults and it is possible that they had a slighter degree of malformation of the tricuspid valve If this interpretation is correct then the demonstration of a severely reduced speed of movement during diastole would indicate a more severe malformation.

The only constant abnormal echocardiographic finding in Ebstein s anomaly has been the delayed tricuspid valve closure compared with the mitral valve closure. This has been found in all reports about echocardiographic findings in Ebstein s anomaly (16, 91 95 96, 150) The asynchrony between tricuspid and mitral closure related to the duration of the QRS-complex shows that this asynchrony for any given QRS-duration is greater for the patients with Ebstein s anomaly than for any other patients studied It has been found that this delayed closure also occurs in the patients with Ebstein s anomaly with type B ventricular preexcitation (VI 150) where the early depolarisation is supposed to be in the right ventricle. These observations suggest that some other factor than delayed depolarisation of the right ventricle is responsible for the delayed tricuspid valve closure. It has been demonstrated that the pressure curve from the right ventricle is abnormal in patients with Ebstein s anomaly (47 150) with a slow initial rise of the pressure and a change to a faster rise of the pressure simultaneous with the mid systolic sound (47) It can be assumed that mechanical factors related to the deformed and displaced tricuspid valve with its large anterior leaflet result in an abnormal right ventricular contraction with a late tricuspid valve closure. A late tricuspid valve closure with a movement of the leaflet towards the right atrium counter acts the pressure rise in the right ventricle until the valve is closed when a more rapid pressure rise can occur Such an explanation of the pressure curve in the right ventricle and the auscultatory events in Ebstein s anomaly was first suggested by Fontana et al. (47) and is supported by the echocardiographic findings in the present investigation.

It has been found that there is a very close time relation between the tricuspid valve closure and the midsystolic sound so often found in patients with Ebstein s anomaly of the tricuspid valve (16 96). Moreover it has been demonstrated that there is a close time relation between the early diastolic sound sometimes found in patients with Ebstein s anomaly and the time of the tricuspid opening (96). A comparison between echocardiography and phonocardiography thus offers an explanation for the common auscultatory events in Ebstein s anomaly

In *conclusion* the following may be stated regarding the echocardiographic findings in Ebstein s anomaly: abnormal echocardiographic findings from the tricuspid valve region have been found in all patients studied The constant and most specific finding has been a delayed tricuspid valve closure. The amplitude of movement of the echo from the anterior tricuspid leaflet is often increased, but may be normal or even reduced. The speed of movement of the echo from the anterior tricuspid leaflet in diastole is often reduced, but may be normal. It is feasible that such a reduced speed of movement and especially a decreased amplitude of movement of the echo from the anterior tricuspid leaflet is a sign of a malformation of greater severity

Combination of echocardiographic data from different regions

It is comparatively rare that the echocardiographic data from one region will give specific

diagnostic information. Usually the echocardiographic information from the different regions have to be evaluated together and related to the results from other investigations such as physical examination, electrocardiography and roentgenography. A few examples suffice to illustrate this. The group of malformations with a hypoplastic left ventricle usually have a rather uniform clinical picture although it is composed of various combinations of a malformation of the aortic valve, the mitral valve and varying degree of hypoplasia of the left ventricle. The echocardiographic examination of the aortic root, the left atrium, the left ventricle and the mitral valve region can provide important diagnostic information and clues as to the type of malformation behind this clinical picture.

In an infant with a large left right shunt and congestive heart failure the demonstration of a large right ventricle and an abnormal septal movement by echocardiography indicates a volume overload of the right ventricle presumably due to a left right shunt at the atrial level. If further echocardiographic examination reveals a left ventricle of normal size but a small left atrium there is good reason to believe that the patient has a total anomalous pulmonary venous drainage. With more detailed information about the patients prior to heart catheterization and angiocardiography these procedures can be directed towards an answer of more specific questions. The time taken for the heart catheterization and angiocardiography can probably thereby be shortened, reducing the risks involved. In some cases, i.e. the hypoplastic left heart syndrome, the need for an invasive investigation may even be eliminated.

Limits to the echocardiographic investigations

The echocardiographic examination can be performed on the majority of infants and children. A few nervous older infants or young children are unwilling to be still during the examination. These children can probably be examined while asleep after a meal or after slight premedication. The neonates can be examined within the incubator.

Interposition of lung tissue in front of the heart usually prohibits the echocardiographic examination as the ultrasonic signal is to a large extent reflected in the boundary between tissue and air and thereby heavily attenuated. This has been encountered in a few patients with obstructive bronchitis.

A severe malformation of the anterior thoracic wall can make the echocardiographic examination difficult to perform because it may be impossible to place and direct the transducer in an appropriate manner.

In adults obesity has presented difficulties in obtaining satisfactory echocardiographic registrations (114). This has not been observed in infants or children.

A malposition of the outflow vessels of the heart can make part of the echocardiographic examination difficult, but recent experiences (20, 58, 146) indicate that the echocardiographic examination can actually aid in identifying these vessels. More experience in unselected material is however needed before this can be established. In malposition of the entire heart the identification of the intracardiac echoes is even more difficult. In order to obtain experience in these often complex malformations the contrast-echo method will be invaluable. Reports on the use of echocardiography in these cases have already appeared (109, 112) but much more information is needed especially in unselected material.

Risks involved in the echocardiographic investigation

Since the ultrasonic energy has well known physical effects on biological tissues (27) the risks involved in its use have of course been discussed and studied. In echocardiography intermittent pulses of ultrasound are used. Since the transducer acts as a transmitter of ultrasonic energy during only 1 μsec and as a receiver during the remaining 999 μsec of the cycle the total exposure time of ultrasonic energy will be short. In studies on the use of ultrasound in the form discussed here no tissue damage or other side-effects have ever been noted (27, 76, 141, 14., 167) and it has been stated that it is unlikely

pattern of movement of the echo from the anterior tricuspid leaflet is abnormal during diastole The observed abnormality is a slow posterior movement during diastole In a few adult patients a normal speed of movement has been found however (69 90 150) The reduced speed of movement might indicate a stenosed tricuspid valve but such an interpretation seems unlikely since no signs of tricuspid stenosis could be found at heart catheterization or angiocardiography in the present material The reason for this reduced speed of movement in diastole is presumably a reduced tricuspid valve flow The few patients with a normal movement of the echo from the anterior tricuspid leaflet during diastole have been adults and it is possible that they had a slighter degree of malformation of the tricuspid valve. If this interpretation is correct then the demonstration of a severely reduced speed of movement during diastole would indicate a more severe malformation.

The only constant abnormal echocardiographic finding in Ebstein s anomaly has been the delayed tricuspid valve closure compared with the mitral valve closure. This has been found in all reports about echocardiographic findings in Ebstein s anomaly (16, 91 95 96, 150) The asynchrony between tricuspid and mitral closure related to the duration of the QRS-complex shows that this asynchrony for any given QRS-duration is greater for the patients with Ebstein s anomaly than for any other patients studied It has been found that this delayed closure also occurs in the patients with Ebstein s anomaly with type B ventricular preexcitation (VI 150) where the early depolarisation is supposed to be in the right ventricle These observations suggest that some other factor than delayed depolarisation of the right ventricle is responsible for the delayed tricuspid valve closure It has been demonstrated that the pressure curve from the right ventricle is abnormal in patients with Ebstein s anomaly (47 150) with a slow initial rise of the pressure and a change to a faster rise of the pressure simultaneous with the midsystolic sound (47). It can be assumed that mechanical factors related to the deformed and displaced tricuspid valve with its large anterior leaflet result in an abnormal right ventricular contraction with a late tricuspid valve closure A late tricuspid valve closure with a movement of the leaflet towards the right atrium counteracts the pressure rise in the right ventricle until the valve is closed when a more rapid pressure rise can occur Such an explanation of the pressure curve in the right ventricle and the auscultatory events in Ebstein s anomaly was first suggested by Fontana et al. (47) and is supported by the echocardiographic findings in the present investigation.

It has been found that there is a very close time relation between the tricuspid valve closure and the midsystolic sound so often found in patients with Ebstein s anomaly of the tricuspid valve (16 96). Moreover it has been demonstrated that there is a close time relation between the early diastolic sound sometimes found in patients with Ebstein s anomaly and the time of the tricuspid opening (96). A comparison between echocardiography and phonocardiography thus offers an explanation for the common auscultatory events in Ebstein s anomaly

In *conclusion* the following may be stated regarding the echocardiographic findings in Ebstein s anomaly abnormal echocardiographic findings from the tricuspid valve region have been found in all patients studied. The constant and most specific finding has been a delayed tricuspid valve closure The amplitude of movement of the echo from the anterior tricuspid leaflet is often increased, but may be normal or even reduced. The speed of movement of the echo from the anterior tricuspid leaflet in diastole is often reduced, but may be normal. It is feasible that such a reduced speed of movement and especially a decreased amplitude of movement of the echo from the anterior tricuspid leaflet is a sign of a malformation of greater severity

Combination of echocardiographic data from different regions

It is comparatively rare that the echocardiographic data from one region will give specific

diagnostic information. Usually the echocardiographic information from the different regions have to be evaluated together and related to the results from other investigations such as physical examination, electrocardiography and roentgenography. A few examples suffice to illustrate this. The group of malformations with a hypoplastic left ventricle usually have a rather uniform clinical picture although it is composed of various combinations of a malformation of the aortic valve, the mitral valve and varying degree of hypoplasia of the left ventricle. The echocardiographic examination of the aortic root, the left atrium, the left ventricle and the mitral valve region can provide important diagnostic information and clues as to the type of malformation behind this clinical picture.

In an infant with a large left-right shunt and congestive heart failure the demonstration of a large right ventricle and an abnormal septal movement by echocardiography indicates a volume overload of the right ventricle presumably due to a left-right shunt at the atrial level. If further echocardiographic examination reveals a left ventricle of normal size but a small left atrium there is good reason to believe that the patient has a total anomalous pulmonary venous drainage. With more detailed information about the patients prior to heart catheterization and angiocardiography these procedures can be directed towards an answer of more specific questions. The time taken for the heart catheterization and angiocardiography can probably thereby be shortened, reducing the risks involved. In some cases, i.e. the hypoplastic left heart syndrome, the need for an invasive investigation may even be eliminated.

Limits to the echocardiographic investigations

The echocardiographic examination can be performed on the majority of infants and children. A few nervous older infants or young children are unwilling to lie still during the examination. These children can probably be examined while asleep after a meal or after slight premedication. The neonates can be examined within the incubator.

Interposition of lung tissue in front of the heart usually prohibits the echocardiographic examination as the ultrasonic signal is to a large extent reflected in the boundary between tissue and air and thereby heavily attenuated. This has been encountered in a few patients with obstructive bronchitis.

A severe malformation of the anterior thoracic wall can make the echocardiographic examination difficult to perform because it may be impossible to place and direct the transducer in an appropriate manner.

In adults obesity has presented difficulties in obtaining satisfactory echocardiographic registrations (114). This has not been observed in infants or children.

A malposition of the outflow vessels of the heart can make part of the echocardiographic examination difficult, but recent experiences (20, 58, 146) indicate that the echocardiographic examination can actually aid in identifying these vessels. More experience in unselected material is however needed before this can be established. In malposition of the entire heart the identification of the intracardiac echoes is even more difficult. In order to obtain experience in these often complex malformations the contrast-echo method will be invaluable. Reports on the use of echocardiography in these cases have already appeared (109, 112) but much more information is needed especially in unselected material.

Risks involved in the echocardiographic investigation

Since the ultrasonic energy has well known physical effects on biological tissues (27) the risks involved in its use have of course been discussed and studied. In echocardiography intermittent pulses of ultrasound are used. Since the transducer acts as a transmitter of ultrasonic energy during only 1 µsec and as a receiver during the remaining 999 µsec of the cycle the total exposure time of ultrasonic energy will be short. In studies on the use of ultrasound in the form discussed here no tissue damage or other side-effects have ever been noted (27, 76, 141, 142, 167) and it has been stated that it is unli

that any complications will arise due to the wide safety margin (167)

Aspects on future use of echocardiography

Echocardiography is now becoming more and more accepted as a useful non-invasive diagnostic method. This is reflected in numerous recent reports about its applications in different diagnostic situations and also in leading articles in several well known medical journals (83 93 159 160) For the immediate further development of this method technical improvements in two fields seem promising. The first is the transducer Improved diagnostic information has resulted from the use of transducers focused to a certain depth (41 60) and from the use of transducers with a higher frequency for the examination of neonates (145) The other field of improvement is the mode of registration. In the past most registrations have been made on Polaroid film. Continuous long registrations have occasionally been used previously (27) but have now received an increasing interest (42, 63) These registrations have been made on film on fibre optic recorders. One advantage of a continuous recording is that there is a greater likelihood of obtaining technically satisfactory recordings in infants and children. The main advantage is, however the possibility of getting a continuous registration while the direction of the transducer is changed ("M-scanning") Thus technique will allow a better demonstration of the anatomical relation between different structures (42, 63).

Another evolution of the use of ultrasound in cardiology has been the search for a two dimensional picture of the heart. This has been made by a scanning technique in different planes (155) called ultrasonocardiotomography or by sector scanning with the transducer on one point on the chest wall (66). Another solution to this problem is based on the "M-scanning" as referred to earlier (65). From this recording images related to the electrocardiogram can be sampled and put together to produce a motion picture. A computer assembly of the prints has also been developed (65) This technique has been called ciné ultrasound cardiography (65). The most recent solution to the problem of obtaining a two dimensional picture of the heart has been developed by Bom (4) who used a transducer with twenty small elements rapidly activated in sequence In this way he could produce instantaneous two-dimensional cross-sectional images of the heart in motion (131 132) This technique has been called multiscan or multi-element echocardiography (131 132). These new techniques are indeed promising. It is, however unlikely that they will replace echocardiography in the way it is used today Further development of these new systems may however lead to their use together with echocardiography and thereby expand the use of ultrasound in practical cardiology

SUMMARY

An echocardiographic study on infants and children has been performed in order to develop and evaluate the echocardiographic technique for clinical practice in pediatrics. The following four regions have been examined (1) the anterior mitral leaflet (2) the aortic root and the left atrium (3) the interventricular septum and the posterior left ventricular wall (4) the anterior tricuspid leaflet.

64 infants and children without heart disease have been examined in order to obtain normal values for different echocardiographic measurements. The reproducibility of the echocardiographic measurements has been tested on 11 infants and children with and without heart disease The reproducibility was found to be adequate for permitting useful comparisons between different patients and between different investigations on the same patient.

In the investigation of the mitral valve region

it was found that a diagnosis of congenital mitral stenosis could be made by echocardiography in older infants and children. The patients with a severe degree of mitral stenosis could be distinguished from those with a slight degree of mitral stenosis. The echocardiographic examination could also be used to evaluate the results of mitral valvotomy. In neonates and young infants a diagnosis of mitral atresia and cor triatriatum could be achieved by echocardiography. In the group of patients with mitral stenosis and varying degree of hypoplasia of the left ventricle the echocardiographic findings could provide additional diagnostic information about the functional state of the mitral valve and the left ventricle.

Echocardiographic measurements of the aortic root diameter and a left atrial dimension were compared with angiocardiographic measurements of the aortic root diameter (148 patients) and the sagittal left atrial diameter (79 patients). In patients with a normally positioned aortic root the diameter measured by the two methods showed a close relation. From the examination of the left atrium it was concluded that the echocardiographic measurement could be used as a semiquantitative measurement of left atrial size.

A comparison between echocardiography and angiocardiography was also made with respect to the size of the left (60 patients) and right (84 patients) ventricles. It was concluded that the echocardiographic distance measurements allows semi-quantitative estimation of the size of the left and right ventricles.

In the echocardiographic examination of the tricuspid valve the study was concentrated on Ebstein's anomaly of the tricuspid valve. It was found that all patients with this anomaly showed an abnormal pattern of movement of the echo from the anterior tricuspid leaflet. This type of abnormal movement has not been found in any other of the patients studied. It seems therefore possible to diagnose Ebstein's anomaly of the tricuspid valve by echocardiography.

The echocardiographic findings from the different regions should be evaluated together and related to the results of other investigations. By means of this procedure it seems likely that more diagnostic information can be gained by non-invasive methods, which is especially desirable in pediatric cardiology.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Ass. Professor Inge Edler who introduced me into the field of echocardiography and who has given me invaluable help and advice throughout this investigation. I am also much indebted to my chief Professor Bertil Lindquist for his generous support and constructive criticism during my work. My thanks are due to my co-author Dr Wigher Mortensson for a very smooth and fruitful cooperation.

During this investigation I have received help from many colleagues and members of the staffs of the Departments of Pediatrics, Thoracic Surgery and the Angiographic Laboratory at the Department of Radiology for which I will express my sincere gratitude. I would especially like to thank Mrs Berith Carlsson for skilful technical assistance, Mrs Christina Lundberg and Miss Britt Jönsson for careful assistance with the patients, Mrs Anne Marie Birke for help with the figures, Mrs Lena Normann for efficient secretary assistance and Miss Roseanne Hughes for reviewing the language of the manuscript.

Last but not least I would like to thank my wife Monica and our children Göran, Staffan and Eva-Kajsa for their patience during the years covered by the study.

This work was supported by grants from the Swedish National Association against Heart and Chest Diseases.

REFERENCES

1 Abbasi, A. S MacAlpin, L. M Eber L. M. & Pearse, M L. Echocardiographic diagnosis of idiopathic hypertrophic cardiomyopathy without outflow obstruction. *Circulation*, *46*. 897 1972.

2 Bleifeld, W & Effert, S.. Über das Ultraschallkardiogramm der Tricuspidalklappe. *Z Kreislaufforsch*, *55* 154 1956.

3 Bolton, M. R., King, J F Reis, R. L., Pugh, D M., Polumbo, R. A., Dunn, M. I. & Mason, D T.. Alterations of echocardiographic features of IHSS by operation: Simultaneous comparison with pre, early and late postoperative catheterizations in the same patients undergoing ventricular septal myectomy *Circulation*, *48 Suppl. IV 47 1973.*

4 Bom, N. New concepts in echocardiography H. E. Stenfert Kroese N V Leiden, 1972.

5 Brown, O R., Harrison, D C. & Popp, R. L.. Echocardiographic study of right ventricular hypertension producing asymmetrical septal hypertrophy *Circulation*, *48*. Suppl. *II* 47 1973

6 Brown, O. R., Popp, R. L. & Harrison, D. C. Improved diagnosis of atrial septal defect and analogous conditions by cardiac echography *Circulation*, *46*, Suppl. *II* 37 1972.

7 Carter W H. & Bowman, C. R.. Estimation of shunt flow in isolated ventricular septal defect by echocardiogram. *Circulation*, *48*. Suppl. *II* 64, *1973*

8 Chesler R., Joffe, H. S., Beck, W & Schrire, V.. Echocardiographic recognition of mitral-semilunar valve discontinuity An aid to the diagnosis of origin of both great vessels from the right ventricle. *Circulation*, *43*. 725 1971

9 Chesler E., Joffe, H. S., Beck, W & Schrire, V Echocardiography in the diagnosis of congenital heart disease. *Pediat Clin N Amer* *18*. 1163 1971

10. Chesler E., Joffe, H. S., Vecht, R., Beck, W & Schrire, V.. Ultrasoundcardiography in single ventricle and the hypoplastic left and right heart syndromes. *Circulation*, *42:* 123 1970.

11 Chung, K. J Alexson, C. G Manning, J A. & Gramiak, R.. Echocardiography in truncus arteriosus. The value of pulmonic valve detection. *Circulation*, *48* 281 1973.

12. Chung, K. J Gramiak, R. & Manning, J A.. Echocardiographic diagnosis of hypertrophic obstructive cardiomyopathy coexisting with fixed left ventricular outflow obstruction in children. *Circulation*, *48*. Suppl. *IV* 126, 1973

13. Chung, K. J Manning, J. A. & Gramiak, R.. Idiopathic hypertrophic cardiomyopathies in infants and children and its differentiation from endocardial fibroelastosis by echocardiography Abstracts from the 11th annual meeting of the Association of European Paediatric Cardiologists, Rhodes, Greece, 1973.

14 Chung, K., Nanda, N. C., Manning, J A. & Gramiak R.. Echocardiographic findings in tetralogy of Fallot. *Amer J Cardiol*, *31* 126, 1973

15. Corya, B. C., Feigenbaum, H., Rasmussen, S. & Black, M J.. Echocardiographic features of congestive cardiomyopathy *Circulation*, *48*. Suppl. *IV* 47 1973

16. Crews, T L., Pridie, R. B., Benham, R. & Leatham, A.. Auscultatory and phonocardiographic findings in Ebstein's anomaly Correlation of first heart sound with ultrasonic records of tricuspid valve movement. *Br Heart J 34* 682, 1972.

17 Davis, R. H., Konecke, L. L., Dillon, J C., Chang, S. & Feigenbaum, H. Echocardiographic findings in discrete subaortic stenosis. *Amer J Cardiol*, *31* 127 1973.

18. DeMaria, A., King, J F Bogren, H., Bonanno, J A., Massumi, R. A., Zelis, R. & Mason, D T The variable spectrum of echocardiographic manifestations of mitral valve prolapse. *Circulation*, *48*. Suppl. *II* 63, 1973

19. Diamond, M. A., Dillon, J C., Haine, C. D Chang, S. & Feigenbaum, H.. Echocardiographic features of atrial septal defect. *Circulation*, *43*. 129 1971

20. Dillon, J C., Feigenbaum, H., Konecke, L. L., Keutel, J Hurwitz, R. A., Davis, R. H. & Chang, S.. Echocardiographic manifestations of d-transposition of the great vessels. *Amer J Cardiol*, *32*. 74 1973

21 Dillon, J C., Haine, C. L., Chang, S. & Feigenbaum, H.. Use of echocardiography in patients with prolapsed mitral valve. *Circulation*, *43*. 503 1971

22. Dillon, J C., Konecke, L. L., Davis, R. H., Chang, S. & Feigenbaum, H. Echocardiographic manifestations of valvular vegetations. *Amer J Cardiol*, *31* 128, 1973.

23. Diamond, W F & Kerber R. E. Mechanism of the echocardiographic abnormality of interventricular septum motion in right ventricular volume overload. *Circulation*, *46*. Suppl. *II* 37 1972.

24. Duchak, J M. Jr Chang, S. & Feigenbaum, H Echocardiographic features of torn chordae tendineae. *Amer J Cardiol*, *29*: 260, 1972.

25. Duchak, J. M., Chang, S. & Feigenbaum, H.. The posterior mitral valve echo and the echocardiographic diagnosis of mitral stenosis. *Amer J Cardiol*, *29* 628, 1972.

26. Edler I.. The diagnostic use of ultrasound in heart disease. *Acta Med Scand*, Suppl. *308* 32, 1955

27 Edler I. The use of ultrasound as a diagnostic aid and its effect on biological tissues. *Acta Med Scand* Suppl. *370*-1961

28. Edler I. Cardiac studies by ultrasound, *in* A. A. Luisada (ed.): *Cardiology an encyclopedia of cardiovascular system, Suppl. 1* McGraw-Hill Book Co., New York 1962.

29 Edler I. The diagnostic use of ultrasound in heart disease, *in* E. Kelly (ed.): *Ultrasonic Energy Biological investigations and medical applications*, University of Illinois Press, Urbana 1965

30. Edler L. Mitral valve function studied by the ultrasound echo method, *in* C. C. Grossman, J. H. Holmes, C. Joyner & E. W Purnell (eds): *Diag-*

nostic ultrasound, Proceedings of the first international conference University of Pittsburgh, 1965 Plenum Press, New York 1966.

31 Edler L. Ultrasoundcardiography in mitral valve stenosis. *Amer J Cardiol, 19*: 18, 1967

32. Edler, I. & Gustafson, A.. Ultrasonic cardiogram in mitral stenosis. *Acta Med Scand, 159*: 85, 1967

33 Edler I., Gustafson, A., Karlefors, T & Christensson, B.. Mitral and aortic valve movements recorded by an ultra-sonic echo method—an experimental study *Acta Med Scand*, Suppl. *370*: 67 1961

34. Edler, I. & Hertz, C. H. Use of ultrasonic reflectoscope for the continuous recording of movements of heart walls. *Kungl Fysiogr Sällsk Lund Förhandl 5* 1 1954.

35 Effert, S.. Der derzeitige Stand der Ultraschallkardiographie. *Arch Kreislaufforsch, 30*: 213 1959

36. Effert, S.. Pre and postoperative evaluation of mitral stenosis by ultrasound. *Amer J Cardiol, 19*: 59 1967

37 Ellis, N., Abbasi, A. S. & Flynn, J J The diagnosis of pericardial effusion in children by the ultrasound M-scan technique. *Excerpta Medica*. Abstracts of papers from the 2nd world congress on ultrasonics in medicine. *277* 10, 1973

38. Eriksson, B. O & Wallentin, I. Personal communication.

39 Feigenbaum, H.. Echocardiographic diagnosis of pericardial effusion. *Amer J Cardiol, 26*. 475, 1970.

40. Feigenbaum, H.. Clinical applications of echocardiography *Progr Cardiovasc Dis 14* 531 1972.

41 Feigenbaum, H.. Echocardiography Lea & Febiger Philadelphia 1972.

42. Feigenbaum, H.. Newer aspects of echocardiography *Circulation, 47* 833 1973.

43 Feigenbaum, H., Popp, R. L., Wolfe, S B., Troy B. L., Pombo, J F Haine, C. L. & Dodge, H. T Ultrasound measurements of the left ventricle. A correlative study with angiocardiography *Arch Int Med, 129*: 461 1972.

44. Feigenbaum, H., Stone, J M., Lee, D A., Nasser W K. & Chang, S. Identification of ultrasound echoes from the left ventricle by use of intracardiac injection of indiocyanine green. *Circulation, 41* 615 1970.

45. Feigenbaum, H., Waldhausen, J A. & Hyde, L. P.. Ultrasound diagnosis of pericardial effusion. *JAMA, 191* 107 1965

46. Fischer J C., Chang, S., Konecke, L. L. & Feigenbaum, H.. Echocardiographic determination of mitral valve flow *Amer J Cardiol, 29*: 262, 1972.

47 Fontana, M. E. & Wooley C. F Sail sound in Ebstein's anomaly of the tricuspid valve. *Circulation, 46*. 155, 1972.

48. Fortuin, N J Hood Jr W P & Craige, E. Evaluation of left ventricular function by echocardiography *Circulation, 46*. 26, 1972.

49 Fry W J Fry F J Kelly E., Fry T A. & Leichner G. H.. Ultrasound transmission in tissue visualization. *In* C. C. Grossman, J H. Holmes, C. Joyner & E. W Purnell (eds.): *Diagnostic ultrasound. Proceedings of the first international conference* University of Pittsburgh, 1965 Plenum Press, New York 1966.

50. Gabor, G E., Winsberg, F & Bloom, H. S. Electrical and mechanical alternation in pericardial effusion. *Chest, 59*: 341 1971.

51 Gan, G T., Tajik, A. J Ritter D G & Schattenberg, T T Echocardiography in children. review of initial experience. *Circulation, 46* Suppl. *II* 154, 1972.

52. Gibson, D G Estimation of left ventricular size by echocardiography *Br Heart J 35* 128 1973.

53 Glaser, J Bharati, S Whitman, V & Liebman, J Echocardiographic findings in patients with anomalous origin of the left coronary artery *Circulation, 48*. Suppl. *II* 63, 1973

54. Glaser J Whitman, V & Liebman, J The differential diagnosis of total anomalous pulmonary drainage in infancy by echocardiography *Circulation, 46*. Suppl. *II* 38, 1972.

55 Goldberg, B. B.. Suprasternal ultrasonography *JAMA, 215* 245, 1971

56. Goldberg, B. B., Ostrum, B. J. & Isard, H. J Ultrasonic determination of pericardial effusion. *JAMA, 202*: 103, 1967

57 Goodman, D J Harrison, D C. & Popp, R. L.. Echocardiographic features of primary pulmonary hypertension. *Circulation, 48*. Suppl. *II* 170, 1973.

58 Gramiak, R., Chung, K. J Nanda N. & Manning, J.. Echocardiographic diagnosis of transposition of the great vessels. *Radiology 106*. 187 1973.

59 Gramiak, R. & Nanda, N. C. Echocardiographic diagnosis of ostium primum septal defect. *Circulation, 46*. Suppl. *II*, 37 1972.

60. Gramiak, R., Nanda, N. C. & Shah, P M Echocardiographic detection of the pulmonary valve. *Radiology 102*. 153 1972.

61 Gramiak, R. & Shah, P M. Echocardiography of the aortic root. *Invest Radiol, 3*. 356, 1968.

62. Gramiak, R. & Shah, P. M.. Echocardiography of the normal and deseased aortic valve. *Radiology 96*. 1 1970.

63 Gramiak, R. & Shah, P M.. Cardiac ultrasonography A review of current applications. *Radiol Clin N Amer 9*: 469 1971

64. Gramiak., R.., Shah., P. M.. & Kramer D. H. Ultrasound cardiography: Contrast studies in anatomy and function. *Radiology 92*. 939 1969

65. Gramiak, R., Waag, R. C. & Simon, W.. Cine ultrasound cardiography *Radiology 107* 175, 1973.

66. Griffith, J. M., Henry W L. & Epstein, S. E. Real time two-dimensional echocardiography *Circulation, 48*. Suppl. *IV* 124, 1973.

67 Gustafson, A.. Ultrasoundcardiography in mitral stenosis. *Acta Med Scand*, Suppl. *461* 1966.

68. Gustafson, A.. Correlation between ultrasoundcardiography hemodynamics and surgical findings in mitral stenosis. *Amer J Cardiol, 19* 32, 1967

69 Gustafson, A. Personal communication.

70. Hagan, A. D & Deely W J Echocardiographic criteria for normal newborn infants. *Amer J Cardiol, 31* 137 1973.

71 Hagan, A., Francis, G., Sahn, D., Karliner J Friedman, W & O'Rourke, R. Systolic anterior

septal motion An unreliable echocardiographic finding. *Circulation, 48.* Suppl. *IV* 173 1973.

72. Henry W L., Clark, C. E. & Epstein, S. E., Asymmetric septal hypertrophy (ASH): Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation, 47* 225 1973

73. Henry W L., Clark, C. E., Glancy D L. & Epstein, S. E.. Echocardiographic measurement of the left ventricular outflow gradient in idiopathic hypertrophic subaortic stenosis. *New Engl J Med, 288* 989 1973

74. Hernberg, J Weiss, B. & Keegan, A.. The ultrasonic recording of aortic valve motion. *Radiology 94* 361 1970.

75. Hertz, C. H Ultrasonic engineering in heart diagnosis. *Amer J Cardiol, 19* 6, 1967

76. Hill, C. R. The possibility of hazard in medical and industrial applications of ultrasound. *Brit J Radiol, 41* 561 1968.

77. Hirata, T., Ozono, I & Nagayama, T.. Estimation of left atrial volumes by ultrasoundcardiography in infants and children. *Med Ultrason, 7* 43, 1969

78. Hirata, T Wolfe, S. B Popp, R. L., Helmen, C. H & Feigenbaum, H. Estimation of left atrial size using ultrasound. *Amer Heart J 78* 43, 1969

79. Horowitz, M. S., Schultz, C. S Stinson, E. B Harrison, D C. & Popp, R. L. Reliability and sensitivity of echocardiography in pericardial effusion. *Circulation, 48.* Suppl. *IV* 125, 1973

80. Jacobi, J Gässler R. & Samlert, H. Neue Ergebnisse mit der Ultraschallkardiographie. *Verh Deutsch Ges Kreislaufforsch, 24* 295 1958.

81. Johnson, M L., Kisslo, J Habersberger P G & Wallace, A. G Echocardiographic evaluation of aortic valvular disease. *Circulation, 48.* Suppl. *II* 46, 1973.

82. Joyner C. R. Experience with ultrasound in the study of heart disease and the production of intra cardiac sound. *In* C. C. Grossman, J H. Holmes, C. Joyner & E. W Purnell (eds.) *Diagnostic ultrasound. Proceeding of the first international conference* University of Pittsburgh, 1965 Plenum Press, New York 1966.

83. Joyner C. R. Echocardiography *Circulation, 46.* 835, 1972.

84. Joyner C. R., Hey E. B., Jr Johnson, J & Reid, J M., Reflected ultrasound in the diagnosis of tricuspid stenosis. *Amer J Cardiol, 19* 66, 1967

85. Joyner C. R. & Reid, J M Ultrasound cardiogram in the selection of patients for mitral valve surgery *Ann N Y Acad Sci, 118.* 512, 1965

86. Kerber R. E., Dippel, W F & Abboud, F M Abnormal motion of the interventricular septum in right ventricular volume overload. Experimental and clinical echocardiographic studies. *Circulation, 48.* 86, 1973

87. Kerber R. E., Isaeff D M & Hancock, E. W.. Echocardiographic patterns in patients with the syndrome of systolic click and late systolic murmur *New Engl J Med, 284* 691 1971

88. Klein, J J & Segal, B. L. Pericardial effusion diagnosed by reflected ultrasound. *Amer J Cardiol, 22:* 57 1968

89. Konecke, L. L., Feigenbaum, H., Chang, S., Corya, B. C. & Fischer J C. Abnormal mitral valve motion in patients with elevated left ventricular diastolic pressures. *Circulation 47* 989 1973

90. Kotler M N. Letter to the Editor *Circulation, 49* 194 1974

91. Kotler M. N & Tabatznik, B.. Recognition of Ebstein's anomaly by ultrasound technique. *Circulation, 44* Suppl. *II* 34, 1971

92. Laurenceau, J L., Guay J M & Gagné, S. Echocardiography in the diagnosis of subaortic membranous stenosis. *Circulation, 48* Suppl. *IV* 46, 1973

93. Lele, P P., Application of ultrasound in medicine. *New Engl J Med, 286.* 1317 1972.

94. Levin, R. R., Frand, M & Baltaxe, H A.. Left atrial enlargement. Correlation of left atrial volume with cardiac series, cine oesophagography and electrocardiography *Radiology 104* 615 1972.

95. Lundstrom, N R. Reflected ultrasound in the diagnosis of congenital heart disease. In *Proceedings of the 1st World Congress on Ultrasonic Diagnostics in Medicine* Vienna, Verlag der Wiener Medizinischer Akademie, 1969 vol. 3

96. Lundström, N R.. Ultrasoundcardiography in the diagnosis of Ebstein's anomaly of the tricuspid valve: Preliminary observations. *Proc Ass Europ Paediatr Cardiol 7* 44 1971

97. Lundström, N. R. Echocardiography in the diagnosis of hypertrophic cardiomyopathy in infants and children. Abstracts from the 11th annual meeting of the Association of Europea Paediatric Cardiologists, Rhodes, Greece, 1973.

98. Lundström, N R.. Letter to the Editor *Circulation, 49:* 194 1974

99. Lundström, N R.. Unpublished data.

100. Lundstrom, N R., & Edler I. Ultrasoundcardiography in infants and children. *Acta Paediat Scand, 60* 117 1971

101. Lundström, N R. & Mortensson, W Ballonerande mitralisklaff som orsak till mitralisinsufficiens hos barn. *Läkartidningen, 69* 4391 1972.

102. McCann, W D Harbold N B., Jr & Giuliani, E. R. The echocardiogram in right ventricula overload. *JAMA 221* 1243, 1972.

103. McDonald, I. G.. Echocardiographic demonstration of bnormal motion of the interventricular septum in left bundle branch block. *Circulation, 48.* 272, 1973

104. McDonald, I. G Feigenbaum, H. & Chang, S Analysis of left ventricular wall motion by reflected ultrasound Application to assessment of myocardial function. *Circulation, 46.* 14 1972.

105. McLaurin, L. P Gibson, T C., Walder W Grossman, W & Craige, E. An appraisal of mitral valve echocardiograms mimicking mitral stenosis in conditions with right ventricular pressure over load. *Circulation, 48* 801 1973

106. Meyer R. A. & Kaplan, S. Echocardiography in the diagnosis of hypoplasia of the left or right ventricle in the neonate. *Circulation, 46.* 55 1972.

107 Meyer R. A. & Kaplan, S. Non-invasive techniques in pediatric cardiovascular disease. *Progr Cardiovasc Dis, 15* 341 1973.

108. Meyer R. A., Schwartz, D C., Benzing III, [redacted] & Kaplan, S.. Ventricular septum in right ventricular overload. An echocardiographic study *Amer J Cardiol 30*: 349 1972.

109 Meyer R., Schwartz, [redacted] Covitz, W & Kaplan, S. Echocardiographic assessment of cardiac malposition. *Excerpta Medica.* Abstracts of papers from the 2nd world congress on ultrasonics [redacted] medicine. *277* 11, 1973.

110. Meyer R. A., Schwartz, D. C. & Kaplan, S. The diagnosis of aortic atresia by echocardiography *Amer J Cardiol, 29* 280 1972.

111 Millward, D K., McLaurin, L. P & Craige, E. Echocardiographic studies of the mitral valv in patients with congestive cardiomyopathy and mitral regurgitation. *Amer Heart J 85* 413, 1973.

112. Minhas, K., Eibl, F & Sofinger R.. Deductive echocardiographic analysis of cardiac malposition complexes in infancy *Excerpta Medica.* Abstracts of papers from the 2nd world congress on ultrasonics in medicine. *277* 11, 1973

113 Moreyra, E., Klein, J J Shimada, H. & Segal, B L. Idiopathic hypertrophic subaortic stenosis diagnosed by reflected ultrasound. *Amer J Cardiol,* 23, 32, 1969

114 Murray J A., Johnston, W & Reid, J M.. Echocardiographic determination of left ventricular dimensions, volumes and performance. *Amer J Cardiol, 30*· 252, 1972.

115 Nanda, N C., Gramiak, R., Shah, P.M., Chung K. J & Robinson, T Echocardiographic diagnosis of pulmonary hypertension. *Excerpta Medica.* Abstracts of papers from the 2nd world congress on ultrasonics in medicine. *277* 12, 1973.

116. Pechstein, J Beitrag zur Ebsteinschen Anomalie der Valvula Tricuspidalis. *Arch Kreislaufforsch, 26* 282, 1957

117 Pieroni, [redacted] R., Freedom, R. M. & Homcy E Echocardiography in atrioventricular canal defects. clinical spectrum. *Excerpta Medica.* Abstracts of papers from the 2nd world congress on ultrasonics in medicine. *277* 12, 1973

118. Pieroni, [redacted] R. Park, S. C., Holbrook, [redacted] R. & Houghton, P B. Echocardiographic diagnosis of septic pericarditis in infancy *J Pediat, 82*: 689 1973.

119 Pombo, J F Troy B L. & Russell, R. O Left ventricular volumes and ejection fraction by echocardiography *Circulation, 43* 480, 1971

120. Popp, R. L A standardized method for manual transducer orientation to obtain left ventricular dimensions. *Excerpta Medica.* Abstracts of papers from the 2nd world congress on ultrasonics in medicine. *277* 13, 1973

121 Popp, R. L Alderman, R. L., Brown, O R. & Harrison, D C. Sources of error in calculation of left ventricular volumes by echocardiography *Amer J Cardiol, 31* 152, 1973.

122. Popp, R L., Brown, O R., Silverman, J & Harrison, D C. Diagnostic use of cardiac echography in the mitral valv prolapse syndromes. *Circulation, 46.* Suppl. *II* 43 1972.

123. Popp R. L. & Harrison, [redacted] C. Ultrasound in the diagnosis and evaluation of therapy of idiopathic hypertrophic subaortic stenosis. *Circulation, 40:* 905 1969

124. Popp, R. L. & Harrison, [redacted] C.. Ultrasonic cardiac echography for determining stroke volume and valvular regurgitation. *Circulation, 42.* 493, 1970.

125 Popp, R. L., Wolfe, S. B., Hirata, T & Feigenbaum, H.. Estimation of right and left ventricular size by ultrasound. A study of the echoes from the inter ventricular septum. *Amer J Cardiol, 24* 523 1969

126. Pridie, R. B.. Left atrial myxomas in childhood. Presentation with emboli-diagnosis by ultrasonics. *Thorax, 27* 759 1972.

127 Pridie, R. B Behnam, R. & Oakley C. M. Echocardiography of the mitral valve in aortic valve disease. *Brit Heart J 33* 296, 1971

128. Pridie, R. B. & Oakley C. Mitral valve movement in hypertrophic obstructive cardiomyopathy *Brit Heart J 31* 390, 1969

129 Pridie, R. B. & Oakley C. M.. Mechanism of mitral regurgitation in hypertrophic obstructive cardiomyopathy *Brit Heart J 32.* 203, 1970.

130 Redwood, D R., Henry W L. & Epstein, S. E. Evaluation of the bility of echocardiography to measure alterations in left ventricular volume. *Circulation, 48.* Suppl. *IV* 206, 1973

131 Roelandt, J Kloster, F ten Cate, F J., Bom, N Lancée, C. T & Hugenholtz, P [redacted] Multiscan echocardiography Description of the system and initial results in 100 patients. *Heart Bulletin, 4* 51 1973

132. Roelandt, J Kloster F Popp, R. L., Pridie, R., Sahn, [redacted] J ten Cate, F J Paladino, D Bom, N. & Hugenholtz, [redacted] G Cooperative evaluating study of multi-element echocardiography *Circulation, 48* Suppl. *IV* 208, 1973.

133 Rothman, J Chase, N E., Kricheff, I. J Mayarat, R. & Berenbaum, E. R. Ultrasonic diagnosis of pericardial effusion. *Circulation, 35* 358, 1967

134. Schmitt, W & Braun, H Ultraschallkardiographie bei angeboren und erworbenen Herzfehlern. *München Med Wschr 103* 523, 1962.

135. Schmitt, W & Braun, H.. *Ultraschallkardiographie* Georg Thieme Verlag, Stuttgart, 1970.

136. Schwartz, D C., Kaplan, S. & Meyer R. A Late systolic mitral regurgitation in children. *Amer J Cardiol 29*· 290, 1972.

137 Segal, B L., Likoff W & Kingsley B. Echocardiography· Clinical application in combined mitral stenosis and mitral regurgitation. *Amer J Cardiol, 19* 42, 1967

138. Shah, P M., Gramiak, R., Adelman, A. G. & Wigle, [redacted] D. Role of echocardiography [redacted] diagnostic nd hemodynamic assessment of hypertrophic subaortic stenosis. *Circulation, 44* 891 1971

139 Shah, P M., Gramiak, R., Adelman, A. G & Wigle, E. D Echocardiographic assessment of the effect of surgery and propanolol on the dynamics of outflow obstruction in HSS. *Circulation, 45.* 516, 1972.

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Printed in Sweden by Almqvist & Wiksell, Uppsala

ACTA PÆDIATRICA SCANDINAVICA SUPPLEMENT 244 1974

STUDIES ON PULMONARY MECHANICS IN INFANTS

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ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 244 1974

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by

Hans Ahlström

LUND 1974

Göteborgs Offsettryckeri AB Kungälv 1974

CONTENTS

The present thesis is based on the following papers.

(I) Pulmonary mechanics in infants. Methodological aspects. Scand J Resp Dis. Accepted for publication. Together with B. Jonson.

(II) Pulmonary mechanics during the first year of life. Scand J Resp Dis. Accepted for publication. Together with B. Jonson.

(III) Pulmonary mechanics in infants surviving severe neonatal respiratory insufficiency. Acta Paediat. Scand. Accepted for publication.

In the text these papers will be quoted as I, II and III.

ABBREVIATIONS

Pulmonary mechanical properties

V_T = tidal volume
V_{IE} = minute ventilation
$\dot{V}$ = air flow rate
Cdyn (l) = dynamic compliance of the lungs
Rf (l) = functional lung resistance
Gf (l) = functional lung conductance
FRC = functional residual volume

Diseases and means of treatment

IRDS = idiopathic respiratory distress syndrome
VSD = ventricular septal defect
PDA = patent ductus arteriosus
CPAP = continuous positive airway pressure
IPPV = intermittent positive pressure ventilation

INTRODUCTION

Besides physical and radiological examination of the chest arterial blood gas analysis is the most important source of diagnostic information about pulmonary disease in infants, making it possible to judge to what extent the lungs fulfil their task as gas exchangers. Decreased arterial oxygen tension and increased carbon dioxide tension indicate pulmonary malfunction but tell us little about its nature. Furthermore pulmonary malfunction during infancy may not be discovered by either physical, radiological or blood gas examinations. For more specific and detailed information of pulmonary disease other investigations must be made. Among these measurements of the mechanical properties of the lungs can give important information concerning some of the conditions necessary for an efficient gas exchange.

Special problems are connected with measurements of pulmonary mechanics in infants since they cannot co-operate and all investigations must be performed during spontaneous breathing at sleep (28, 36).

Several methods for investigations of pulmonary mechanics in infants are described earlier (8, 9, 22, 24, 25, 33, 48), but most methods are designed for newborn infants. These methods cannot be used in older infants, without considerable modifications including sedation. Sedation is apt to produce unphysiological conditions and may even be dangerous in infants with pulmonary disease. The forced oscillatory method (48) can be used without sedation after the neonatal period. This method gives a measure of the resistance of the lungs and the thoracic and abdominal wall, but no specific information on pulmonary compliance. The results obtained are therefore somewhat difficult to interpret and they are not fully comparable with the usual measurements of pulmonary mechanics.

Earlier described methods including measurements of the oesophageal pressure are time-consuming and can hardly be used as routine procedures. Great experience is needed in the choice of "representative breaths" for manual calculations of pulmonary mechanics. These methods have therefore been used mainly for scientific purposes.

A method for investigation of mechanical properties of the lungs must first of all be non-hazardous. It should serve several purposes

1) As a diagnostic tool in the investigation of even severely ill infants, with different types of pulmonary disease
2) For the follow-up of infants who had severe pulmonary disease during the neonatal period
3) For evaluations of the effect of surgical or pharmacological therapeutical procedures.
4) For scientific purposes e.g. to provide a better understanding of the pulmonary physiology of the normal infant and the infant with pulmonary disease

A new method for studies of pulmonary mechanics in infants is presented (I) which attempts to solve some of the specific methodological problems connected with investigations of infants *after* the neonatal period. Several of these problems will be discussed here. Different applications of the method will be described. The method has been found convenient enough to be used in clinical routine

METHODOLOGICAL PROBLEMS

1 Security considerations

A method designed for clinical use in the investigation of infants who may be critically ill in ventilatory insufficiency must not involve risks of deterioration of the condition. If the ventilatory reserves are small procedures leading to decreased ventilatory ability are potentially hazardous. It is naturally of utmost importance that all risks are considered, when a new method for investigation of pulmonary mechanics is introduced. The need for gentle handling and great patience in the investigation of infants is wellknown to every pediatrician.

A prerequisite for proper evaluation of pulmonary mechanics in infants is that the investigation is performed at rest and preferably at sleep (28, 36). To achieve this sedatives have been used in all previous studies, including measurements of the oesophageal pressure in infants after the neonatal period (9, 24, 33). Sedatives were avoided in the present study for two main reasons

1) Most sedatives have a depressive effect on the respiration, which is obviously hazardous in the investigation of infants with ventilatory insufficiency
2) Sedatives may influence the breathing and the information on pulmonary mechanics would then be "unphysiological" (36)

If the infants have been deprivated of sleep for 2–7 hours and newly fed the investigation can be performed on the sleeping infant without the use of sedatives if suitable equipment for measurements of oesophageal pressure and air flow rate is used (I). Feeding does not have any adverse effect on the respiratory mechanics in newborn infants (40).

In most previous measurements of oesophageal pressure in infants balloon catheters have been used. After several trials we abandoned the use of balloon catheters in favour of fluid filled catheters (I). In non-sedated infants it was found that a thin polyethylene catheter was more suitable than a balloon catheter, which is inevitably coarser and more rigid. The catheter was easily introduced through the nose without much irritation of the infant. Local anaesthesia of the mucous membranes of the nose or the pharynx was not necessary. This is advantageous since local anaesthesia of the upper airways increases the risk of aspiration. As the infants were newly fed the risk of vomiting must be considered even with the thin oesophageal catheter used.

Vomiting in an infant in supine position with the face fixed in a sealing diaphragm may be dangerous, especially in infants with respiratory distress. The described body plethysmograph for measurement of air flow rate (I) is constructed so that an infant can be taken out of it, within a few seconds if vomiting or other complications should occur. Equipment for suction, oxygen administration, and positive pressure ventilation should be close at hand during the investigation. A physician trained in the care of sick infants must be present throughout the investigation.

During our preliminary studies with a balloon catheter vomiting occurred several times, whereas in about 200 investigations with a fluid filled catheter, only one infant (with gastro-enteritis) vomited.

Infants with severe ventilatory insufficiency cannot be transported to a laboratory for examination without considerable risks of deterioration of the condition. A modification of the described method for studies of pulmonary mechanics makes examination of these infants possible. A face chamber originally made for the treatment of infants with idiopathic respiratory distress syndrome (1) was used (fig. 1). This is a cylinder with a sealing diaphragm of the same model as the one

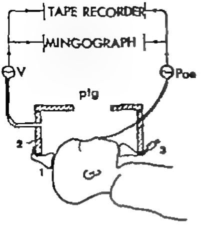

Fig 1 Equipment for bedside studies of pulmonary mechanics with face chamber V and Poe indicate transducers for pressure and flow measurements. Pig indicates the pneumotachograph screen in the lid of the face chamber The face chamber is placed around the sealing diaphragm, 1 attached to the cylindrical face chamber, 2. The air is evacuated from the sealing diaphragm through the tube, 3

used in the body plethysmograph. In the lid of the cylinder a pneumotachograph screen was mounted. The face chamber was attached to a stage with the infant s face protruding through the sealing diaphragm into the face chamber An oesophageal catheter was gently introduced and passed out through the face chamber and connected to the pressure transducer The signals for oesophageal pressure and air flow rate were fed to a tape recorder (Analog 7 Philips) and a direct writing recorder (Mingograph 81 Siemens-Elema). Instead of using carbon dioxide for hyperventilation, which was considered risky the infants were rebreathing dead space air of the face chamber for about two minutes. After the investigation the tape recorded data were analyzed by the computer as in the original method (1)

As this equipment for measurements of air flow rate does not measure compression and decompression of gas within the thorax the obtained values are not exactly comparable to normal data obtained with the original method They seem, however sufficient for an evaluation of the pulmonary properties in severely ill infants. An example will be given of the investigation of an infant with severe respiratory insufficiency (page 16).

In the studies of newborn infants, who are kept in incubators, investigation with the face chamber method seems to be the most suitable An optimal environment with respect to temperature and humidity will be better provided within an incubator than in the body plethysmograph.

2. *Standardization procedures*

In the investigation of pulmonary mechanics in adults, voluntary hyperventilation, special breathing patterns such as panting and regulation of air flow rate are examples of ways to standardize the breathing pattern. Obtained values of compliance are related to the lung volume resistance to the airflow and so on In infants these procedures are not possible and other forms of standardization of the procedure must be made to obtain reliable and reproducible values of pulmonary mechanics.

For adequate comparisons between different infants and between one and the same infant investigated on different occasions, standardized conditions of the examinations are necessary During *sleep* rather basal conditions in most infants can be assumed However it is difficult to evaluate the depth of the sleep of an infant during the investigation. High breathing frequency at rest may be a sign of excitation. In most normal infants a moderate increase of the breathing frequency was seen at increasing minute ventilation during carbon dioxide hyperventilation In some infants *decreasing* breathing frequency was found during carbon dioxide exposure and a further decrease in frequency occurred after the cessation of carbon dioxide. This pattern may indicate that basal conditions were not present in the beginning of the investigation.

In a non-sedated infant the equipment must not disturb the infant's sleep. It appears that the infants are very sensitive to any tactile stimulus on the area around the nose and the mouth. The sealing diaphragm of the body plethysmograph does not press on the infant s face One important factor for the comfort of the infants is that the plethysmograph is air conditioned with respect to temperature and humidity The investigations were performed in semidarkness.

The use of *nose drops* did not significantly change pulmonary mechanics in normal infants (1) but may contribute to the standardization in reducing the nasal resistance particularly in infants with respiratory infections. The concentration of the nose drops (oxymetazolin 0 1 mg/ml, Nezeril®) was so low that any effects on the bronchi

and the central nervous system could be excluded (17)

Studies in adults have shown that *hyperventilation* is one way of standardizing the breathing pattern (12 29). During carbon dioxide induced hyperventilation a closer correlation of Cdyn(l) *and log Gf(l) to body size measures was found* than at rest in studies of normal infants (II). This makes the use of data obtained at hyperventilation preferable

In some infants especially those prematurely *born, the breathing is irregular with repeated short* periods of apnoea – "periodic breathing" Measurement at rest is sometimes not possible in these infants (III) After exposition to 5 per cent carbon *dioxide in oxygen the breathing became regular within one minute This regularization of breathing* may be due to both the increased carbon dioxide concentration and the high oxygen content in the inspired gas (7 11 23).

In most previous studies on pulmonary mechanics during infancy the calculations have been made manually from recordings of pressure volume and flow The use of *computerized calculations* has several advantages. The calculations are *free from bias.* The large amount of primary *information included in one recording makes the* measurements *less sensitive to variations in the breathing pattern* (I) The results are immediately available which is of importance in the diagnostic use of the method

3 Sources of errors in the measurement of pulmonary mechanics in infants

In infants, lung compliance must be measured during dynamic conditions since the infants cannot hold their breath

Cdyn(l) = $V_T/\Delta P$ where Cdyn(l) is dynamic compliance V_T the tidal volume and ΔP is the pressure change between the moments when the airflow is zero before and after every inspiration *It is obvious that one prerequisite for correct* measurement of Cdyn(l) is that the pressure and flow signals are recorded *without phase shift* The equipment used in the present study was carefully controlled in this respect (I) Even small phase shifts between *flow and pressure were found to* cause considerable errors in the obtained values of Cdyn(l) especially in infants with a high breathing frequency and high pulmonary resistance (fig. 2)

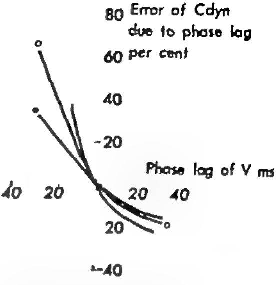

Fig. 2. Errors caused by phase lag in values of Cdyn(l) in per cent of true values. Positive values on abscissa means that flow rate, $\dot{V}$ lags behind pressure.
- ● normal infant, *Rf(l)* 21 7 cm H_2O/ (l/) 47 breaths/min.
- ○ *infant with obstructive bronchitis, Rf(l)* 108 cm H_2O/ (l/s) 33 breaths/min.
- x infants with ventricular septal defect, *Rf(l)* 46 4 cm H_2O/ (l/s), 141 breaths/min.

Small airbubbles within the catheter and the transducer may cause considerable phase shifts. When using a fluid filled system for the pressure recording, free air will be released at body temperature from the fluid if this is saturated with air at room temperature Repeated flushing may even *increase the amount of air released from the fluid* The frequency response of such a system will be very variable and it is obviously not possible to compensate for this phase lag e.g. by electrical means By using *boiled water* the problems of dissolved air is eliminated *In fact* air adhering to the walls of the catheter will rather be dissolved The catheter transducer system must be carefully flushed before the investigation and repeatedly during it to prevent the holes of the tip of the catheter to be occluded by the oesophageal wall or mucus.

According to Senterre and Guebelle (41) fluid filled catheters are unsuitable in the measurements of the oesophageal pressure because of the *great amplitude variations* at *different frequencies. Their* recording system was obviously not suitable With the equipment used in this work a correct response could be obtained up to 60 Hertz. The signals were

electrically damped to give the same frequency response as the body plethysmograph.

The recording from a body plethysmograph is sensitive to *transient pressure variations* in the room. The compensation chamber (42) connected to the transducer eliminates these errors. The compensation chamber is connected to the secondary side of the transducer and is open to the room via a screen pneumotachograph. The volume of the compensation chamber is adjusted to give the same time constant as that of the body plethysmograph.

Leaks in the body plethysmograph give false values of the volume and flow recordings. The tightness of the body plethysmograph used was tested by feeding a known airflow into it, first without an infant when the hole for the infant's face was covered by a lid, and later during the actual investigation with the infant in proper position. The resulting signals should be the same if the system was tight.

STUDIES OF PULMONARY MECHANICS IN NORMAL INFANTS

26 infants without heart and lung diseases were studied (II). Data of V_T, V_{IE}, Cdyn(l), and Gf(l) were closely correlated to body size measures. Generally our data were in agreement with those of other authors (9, 24, 33, 48). Correlation to height was found suitable in comparisons with sick infants (II, III). From the formula for linear regression the expected values for some properties of pulmonary mechanics from infants between 40 and 75 cm are calculated (Table 1). As the equation for regression between Gf(l) and height is logaritmic (II) the values of ± 1 and 2 SD are given to allow easy estimate of the conductance values of an infant.

Table 1. *Mechanical properties of the lungs related to height*

Height cm	V_T ml	V_{IE} l/min	Cdyn(l) ml/cm H_2O	Gf(l) (l/s)/cm H_2O −2 SD	−1 SD	mean	+1 SD	+2 SD
40	8.5	0.68	4.2	0.010	0.014	0.019	0.027	0.037
41	10.0	0.72	4.4	0.010	0.014	0.020	0.028	0.039
42	11.5	0.76	4.5	0.011	0.015	0.021	0.029	0.040
43	13.0	0.80	4.6	0.011	0.015	0.021	0.029	0.041
44	14.5	0.84	4.8	0.011	0.016	0.022	0.030	0.042
45	16.0	0.88	4.9	0.012	0.016	0.022	0.031	0.043
46	17.5	0.92	5.1	0.012	0.016	0.023	0.032	0.044
47	19.0	0.96	5.2	0.012	0.017	0.024	0.033	0.045
48	20.4	1.00	5.4	0.013	0.017	0.024	0.034	0.047
49	21.9	1.04	5.5	0.013	0.018	0.025	0.035	0.048
50	23.4	1.08	5.7	0.013	0.018	0.026	0.036	0.049
51	24.9	1.12	5.8	0.014	0.019	0.026	0.037	0.051
52	26.4	1.16	6.0	0.014	0.019	0.027	0.038	0.052
53	27.9	1.20	6.1	0.014	0.020	0.028	0.039	0.054
54	29.4	1.24	6.3	0.015	0.021	0.029	0.040	0.055
55	30.9	1.28	6.4	0.015	0.021	0.029	0.041	0.057
56	32.4	1.32	6.5	0.016	0.022	0.030	0.042	0.058
57	33.9	1.36	6.7	0.016	0.022	0.031	0.043	0.060
58	35.4	1.40	6.8	0.017	0.023	0.032	0.044	0.062
59	36.9	1.44	7.0	0.017	0.024	0.033	0.046	0.063
60	38.4	1.48	7.1	0.017	0.024	0.034	0.047	0.065
61	39.9	1.52	7.3	0.018	0.025	0.035	0.048	0.067
62	41.4	1.56	7.4	0.018	0.026	0.036	0.050	0.069
63	42.9	1.61	7.6	0.019	0.026	0.037	0.051	0.071
64	44.3	1.65	7.7	0.019	0.027	0.038	0.052	0.073
65	45.8	1.69	7.9	0.020	0.028	0.039	0.054	0.075
66	47.3	1.73	8.0	0.021	0.029	0.040	0.055	0.077
67	48.8	1.77	8.2	0.021	0.029	0.041	0.057	0.079
68	50.3	1.81	8.3	0.022	0.030	0.042	0.058	0.081
69	51.8	1.85	8.4	0.022	0.031	0.043	0.060	0.084
70	53.3	1.89	8.6	0.023	0.032	0.044	0.062	0.086
71	54.8	1.93	8.7	0.024	0.033	0.046	0.064	0.088
72	56.3	1.97	8.9	0.024	0.034	0.047	0.065	0.091
73	57.8	2.01	9.0	0.025	0.035	0.048	0.067	0.093
74	59.3	2.05	9.2	0.026	0.036	0.050	0.069	0.096
75	60.8	2.09	9.3	0.026	0.037	0.051	0.071	0.099
SD:	±7.8	±0.3	±1.6					

It could be suspected that pulmonary properties such as compliance and conductance would not be a linear function of the *height* but rather vary *exponentially* e.g. with height[3] i.e. a volume measure. However in this sample of normal infants the closest correlations were found to the more primary measurements. It must, however be stressed that these calculations are based upon measurements of infants, who generally were below 70 cm. In higher infants correlations to exponential functions of body size measures may be better (II). This may explain why some other authors (9, 33) have found higher values of e.g. V_T, $\dot{V}_{IE}$ and Cdyn(l) in some large infants than would be expected from our data. In the studies of infants recovering from severe neonatal ventilatory insufficiency (III) some values of e.g. Cdyn(l) in large infants were higher than expected in relation to the normal values, presented in paper II. This thus does not necessarily mean that these infants have abnormal elastic properties of the lungs (see page 14).

STUDIES OF PULMONARY MECHANICS IN DISEASED INFANTS

1 Interpretation of data from diseased infants

Recording of the *breathing frequency* is probably the most used simple test in evaluating diseases of the chest in infants. Tachypnoea occurs both in obstructive airway disease and conditions characterized by a low pulmonary compliance Increasing breathing frequency may also be a valuable sign of deterioration of the infant s condition. The value of recording the breathing frequency repeatedly in diseased infants is thus indisputable However isolated values of the breathing frequency e.g. obtained during measurements of pulmonary mechanics are of minor value Also normal infants without heart or lung disease could occasionally have a high breathing frequency even during sleep (I) Similar results are reported by other authors studying pulmonary mechanics in infancy (24 33).

Data on *tidal volume* and *minute ventilation* seem to give little if any information in the evaluation of pulmonary function in hitherto studied groups of patients Attempts to obtain reproducible values of thoracic gas volume (e.g. FRC) failed (I) as a non-sedated infant immediately wakes up and moves when the mouth and nose are occluded. Other authors, who have studied thoracic gas volume in infants after the neonatal period have been forced to use more or less heavy sedation (9 33).

Studies of *Cdyn(l)* have proved to give valuable information on the mechanical properties of the lungs (III) However the interpretation of the values of Cdyn(l) in diseased infants is sometimes difficult. A low value of Cdyn(l) does not mean that the lungs are abnormally stiff if the airways are obstructed (III). It is known that such a decreased value of Cdyn(l) occurs in obstructive lung disease particularly at *high breathing frequencies*. This phenomenon of frequency dependent compliance has been thoroughly analysed by Otis et al. (32). If some airways close because of airway disease the values of Cdyn(l) may further decrease (21)

During infancy many diseases give an increased pulmonary resistance Measurements of *pulmonary resistance* or *conductance* may thus be of importance in the evaluation of the lung function in infants with cardio-pulmonary diseases The *functional resistance* is calculated from the measured work rate against the pulmonary resistance and the ventilation (20 II). This work comprises work associated with flow in and out through the lungs, and work to overcome tissue viscosity Roughly similar values of Rf(l) are obtained at varying ventilation (I) This independency of ventilation makes Rf(l) particularly useful as it allows comparisons between observations at different ventilation volumes.

In most infants the obtained values of Rf(l) or Gf(l) are sufficient for an adequate evaluation of the patency of the airway If either of these values is abnormal additional information may be obtained from studies of the form of pressure-flow or pressure-volume loops (13 19 I). Thus a pressure flow loop may show e g high resistance at the end of the inspiration which may indicate an extrathoracic airway obstruction (III). Several authors have used the pressure-flow loops for actual measurements of e.g. inspiratory and expiratory resistance assuming that the elastic recoil pressure has a linear relation to the lung volume This is not reasonable in infants with pulmonary disease (I) From the pressure flow loops the resistance values at zero flow can also be calculated (1). This is done under the assumption that the pressures associated with inertia of the lungs and airway gas are so small that they can be disregarded (22, 35 36) The zero resistance values give principally information on the patency of the airways at zero flow i e during "static conditions (I) Together with the computer calculated values, these zero flow resistance values make it possible to compare different infants numerically Numerical values are also useful in follow-up studies.

2. Studies of pulmonary mechanics after neonatal respiratory insufficiency

The use of intermittent positive pressure ventilation (IPPV) and continuous positive airway pressure (CPAP) in the treatment of ventilatory insufficiency in the neonatal period has increased the survival rate dramatically. Some survivors have however, pulmonary symptoms for a long time after the cessation of the ventilatory support. Several authors have discussed the reasons for these symptoms (3, 4, 27, 30, 31, 38, 44, 45) but few studies of the pulmonary function have been made (2, 10, 43).

Ventilators for IPPV have been used in the neonatal unit in Lund since 1969. After the encouraging report by Gregory et al. (14) concerning treatment of idiopathic respiratory distress syndrome (IRDS) with CPAP this method was introduced.

The use of an indwelling tracheal tube has several disadvantages:

1) The tube may damage the mucous membranes in the upper airways resulting in decreased ciliary function and stagnation of mucus in the airways (39).
2) The risk of pulmonary infection is increased.
3) The tube can suddenly be occluded by mucus.
4) Endotracheal tubes seem to be a prerequisite for the development of bronchopulmonary dysplasia (44).

Because of these potential hazards CPAP treatment via an endotracheal tube seems justifiable only in infants with *severe* ventilatory insufficiency due to IRDS. The risk of apnoea and secondary intracranial ischaemic damages is in these infants considerably increased.

The grunting phenomenon seen in infants with IRDS may be regarded as an attempt to prevent alveolar collapse at the start of every expiration by elevating the transpulmonary pressure (16). The ability of grunting is lost when the infant is intubated. If the continuous positive pressure accidently decreases the risk of severe deterioration in the condition of the intubated infant is considerable. This is a further argument against intubation.

The head chamber suggested by Gregory et al. (14) for CPAP treatment without intubation was not found suitable because of the risk of congestion of the veins of the neck, which has been found hazardous (46). Furthermore the head chamber provides poor access to the upper airways in emergencies. The risk of cochlear damage because of the noise level in a head chamber must also be considered (5).

The *face chamber* described earlier (page 6) was constructed. Because of the good results in the treatment of IRDS with this device (1) the use of IPPV in IRDS was abandoned in our neonatal unit except for those occasions when the infants have sudden apnoeic spells. In ventilatory insufficiency due to postasphyxia syndrome and respiratory insufficiency syndrome IPPV is still the therapy of choice. In the faciliation of weaning from IPPV in these infants, and to shorten the time of IPPV, CPAP via a face chamber is also very convenient.

A prospective survey of pulmonary mechanics of 24 infants surviving three types of ventilatory insufficiency was made (III).

1) 15 infants had *idiopathic respiratory distress syndrome*. The diagnosis was based upon clinical criteria (i.e. grunting, retractions and tachypnoea) and a $P_aO_2 < 70$ mm Hg when breathing 100 per cent oxygen (hyperoxia test). A radiological reticulogranular picture was considered as supportive for the diagnosis.
2) 6 infants had reccurrent apnoea in the prematurity (*respiratory insufficiency syndrome*). This syndrome is chiefly seen in small prematures, with an apparently normal lung function during the first day(s) of life. Apnoeic spells with bradycardia, possible due to cerebral immaturity makes ventilatory support necessary.
3) 3 infants suffered from the *postasphyxia syndrome* (37), which is seen in fullterm as well as in preterm infants. The ventilatory insufficiency is due to an intrauterine asphyxia often in combination with aspiration of amniotic fluid. Due to hypoxia and acidosis the normal adjustment of the circulation after birth will be impaired with subsequent right-to-left shunting of the blood either in the lungs or via a patent ductus arteriosus. At hyperoxia test a poor increase of P_aO_2 is found.

In follow-up studies of 20 of the 24 infants surviving severe neonatal ventilatory insufficiency

it was found that early measurement of pulmonary conductance was a valuable tool for prognostic evaluation as concerns pulmonary symptoms later during infancy. A valid comparison of the different treatments could not be made since the groups with IRDS were not comparable as to the severity of the disease (III). However, no infant treated with CPAP via a face chamber had any clinical pulmonary sequelae at the follow up studies. IPPV treatment of long duration (i.e. >200 hours) was associated with low values of Cdyn(l) and Gf(l) at the initial investigation. Most infants IPPV treated for long periods of time later developed clinical respiratory symptoms. One infant CPAP treated via an endotracheal tube and breathing high oxygen concentration for several days had gross pulmonary abnormalities and clinical symptoms during the first year of life suggesting broncho-pulmonary dysplasia.

Independent of diagnosis and way of treatment a general trend towards low Gf(l) in relation to height was found at the follow-up studies. Bronchospasm, increased susceptibility to airway infection due to the prematurity or true sequelae from the primary disease may all contribute to this tendency towards airway obstruction.

The high values of Cdyn(l) at the reinvestigations in infants higher than 60 cm do not necessarily indicate pulmonary malfunction (see page 11). In fact, when comparing Cdyn(l) of normal infants (II) higher than 60 cm with those of corresponding height in this investigation no statistically significant difference was found.

The method described for measurements of pulmonary mechanics was found very suitable for this type of study. Information of prognostic value is obtained and comparisons between different therapeutical approaches to pulmonary diseases and their effect on pulmonary mechanics can be made in the future.

3. Studies of pulmonary mechanics in infants with cardio-vascular left-to-right shunts

Some of the main features in the clinical picture of infants with congestive heart failure are of respiratory nature. Thus tachypnoea and sternal and intercostal retractions are dominating symptoms especially in infants with a left-to-right shunt via a ventricular septal defect (VSD) or a patent ductus arteriosus (PDA). These symptoms can be supposed to be correlated to the magnitude of the shunt as well as to the pressures in the pulmonary circulation. In addition these infants have an increased susceptibility to airway infections which sometimes may lead to severe obstructive symptoms.

It can be assumed that any disturbance of the heart function and the intrapulmonary circulation disturbs the mechanical properties of the lungs to a certain extent. In adults with cardiac disease many studies of pulmonary mechanics have been performed but few investigations have been done on infants (15, 18, 47). The presented method for measurement of pulmonary mechanics was found suitable for investigation of infants with congenital heart defects. To illustrate this use of the method some preliminary results will be given.

19 infants with cardio-vascular left-to-right shunts verified by cardiac catheterisation were studied. 4 infants had PDA and 15 VSD. Pulmonary artery pressure was increased, mostly due to the increased blood flow. The pulmonary vascular resistance was normal in 18 and slightly elevated in one infant. Pulmonary mechanics were measured just before or after the time of the cardiac catheterisation and several infants were reinvestigated at one or more occasions during the first year of life. All infants with PDA were operated on and pulmonary mechanics was reinvestigated. The absence of cardiac murmurs and a decreasing roentgenological heart volume were taken as reliable signs of a successful operation.

In agreement with other authors (15, 18, 47) it was found that Cdyn(l) generally was decreased compared to normal infants (fig. 3). Though the infants with left-to-right shunts as a group had significantly lower values of Cdyn(l) than expected ($p<0.001$), 9 of them had values within the normal range. Out of these, two infants with large shunts but with a moderate increase of the pulmonary artery pressure had higher values of Cdyn(l) than predicted.

A significant correlation between the reduction in Cdyn(l) and the mean pulmonary artery pressure was found (fig. 4). Wallgren et al. (47) and Howlett (18) who have investigated pulmonary mechanics in infants with various types of congenital heart defects were not able to find such a correlation. Griffin et al. (15) who studied infants with isolated VSD and PDA found a significant

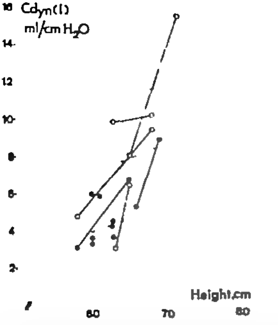

Fig. 3 Cdyn(l) in relation to height. The dotted lines indicate the expected value ± 2 SD (11). Values before and after closure of a PDA or pulmonary banding in VSD, are connected with lines.
● ventricular septal defect.
○ patent ductus arteriosus.

correlation between the peak pulmonary artery pressure and Cdyn(l) They suggested that serial measurements of pulmonary compliance in infants with congenital heart defects could give important prognostic information. The results from serial measurements in the present study do not confirm this suggestion Clinical improvements or deteriorations were not significantly correlated to changes in Cdyn(1).

After closure of PDA a significant increase of Cdyn(l) was found in three of the four investigated infants (fig. 3). In three infants with VSD pulmonary banding was performed because of repeated severe obstructive airway disease in combination with pulmonary hypertension and congestive heart failure One infant died An increase of Cdyn(l) was found in the other two (fig. 3)

In spite of the high incidence of obstructive airway disease in infants with large left-to-right shunts and elevated pulmonary artery pressure the obtained values of Gf(1) were in general not decreased In fact, many infants even those with huge shunts and significant pulmonary hypertension had *higher* values of Gf(l) than expected In some infants the conductance values varied considerably during the investigation The pressure flow loops were generally normal with normal endexpiratory and endinspiratory resistance values.

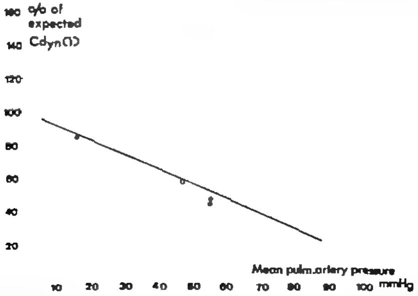

Fig. 4 Correlation between obtained values of Cdyn(l) in per cent of the expected ones and mean pulmonary artery pressure. The regression line y = 102.4 – 0.9 x is drawn. The correlation is significant, $p < 0.01$ $r = -0.60$ Symbols: see fig. 3

However during manifest airway infection with bronchial obstruction the values of Gf(l) decrease considerably The previously low values of Cdyn(l) decrease further and the infants may be critically ill in severe respiratory insufficiency

Fig 5 shows the pressure-flow loops from a 3 1/2 months old infant with VSD and a large left-to-right shunt and pulmonary hypertension. At the first investigation it had signs of congestive heart failure with tachypnoea, intercostal retractions and moderate liver enlargement. Measurement of pulmonary mechanics revealed an increased minute ventilation a low Cdyn(l) and a normal Gf(l). During an airway infection one week later the infant s condition rapidly deteriorated Reinvestigation of pulmonary mechanics was performed with the modificated mobile equipment described above A remarkable decrease of both the values of Cdyn(l) and Gf(l) was found Due to severe pulmonary insufficiency the infant was treated with CPAP via a face chamber (1) A dramatic improvement of the condition of the infant was found during spontaneous breathing against a continuous positive pressure of 6–8 cm H_2O After one week of CPAP treatment the infant was referred to the clinic of thoracic surgery for pulmonary banding. Unfortunately the infant died two weeks later due to postoperative complications.

As all data of the infants with cardiac left-to-right shunts are not yet completely analyzed the reasons for the changes in the pulmonary mechanics in these infants can at the present not be fully discussed. Obviously the combination of a decrease of Gf(l) during airway obstruction e g due to infections, associated with a further decrease of Cdyn(l) gives rise to an enormous increase of the work of breathing. The risk of severe deterioration and respiratory and circulatory insufficiency is considerable It is well known that infants with large left-to-right shunts may need IPPV and/or urgent surgical intervention to combat congestive

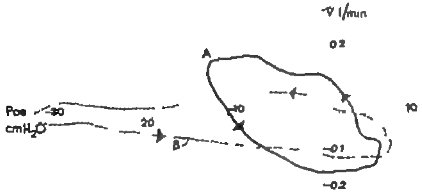

Fig. 5 Pressure-flow loops in an infant with VSD and pulmonary hypertension. The loops run counterclockwise indicated by arrows. Positive flow values: inspiration. Loop A is obtained at the initial investigation during moderate congestive heart failure and is apart from low Cdyn(l) normal. Loop B is obtained at the reinvestigation during ventilatory insufficiency 10 days later during an airway infection. There are excessive respiratory variations in the oesophageal pressure, reflecting low Gf(l) and Cdyn(l) values.

	Cdyn(l) ml/cm H_2O	Gf(l) (l/s)/cm H_2O
Expected value:	7.3	0.034
Initial investigation:	3 7	0 031
Reinvestigation:	0.53	0.004

heart failure during obstructive airway diseases. CPAP treatment without intubation seems to be an efficient and less harmful alternative to IPPV. During CPAP breathing the infection may be cured and surgical intervention may be delayed. During such therapy repeated measurements of pulmonary mechanics could be of diagnostic and prognostic value. The face chamber is thus useful both as a therapeutical and a diagnostic tool.

GENERAL DISCUSSION

As pulmonary disease is one of the most frequent causes of illness in infancy the need of specific and sensitive methods for pulmonary investigations is obvious. Earlier described methods for studies of pulmonary mechanics have several disadvantages discussed above and most of them cannot be used in clinical routine investigations. The presented method fulfils reasonable demands on a safe and reliable method for such studies in infancy

The method was proved to provide valuable information in the investigation of diseased infants. It could be used as a prognostic tool for the evaluation of infants with previous pulmonary diseases. Such studies can give information on the nature of the pulmonary malfunction with great use for decisions on therapy The method can also be used for diagnosis of pulmonary or cardiac disease with obscure pulmonary symptoms. Evaluation of different therapeutical approaches to pulmonary disease is possible The effect of drugs on pulmonary mechanics can thus easily be studied (III) This method for a more objective information on pharmacological effects in human infants may also be of importance in severe forms of chronic pulmonary disease in infants e.g bronchial asthma and cystic fibrosis, which usually give symptoms during infancy (26). An early efficient evaluation of the lung function and possible effects of different drugs may be of great prognostic value It is likely that many of these infants although clinically healthy during certain periods nevertheless have subclinical signs of pulmonary malfunction only detectable with specific methods, such as the one presented here

With suitable modifications, described above the method may well be applicable during the neonatal period with its various forms of pulmonary diseases. It may further be possible in the future to let the computer take over more of the analysis of the available data. When more experience has been gained on various breathing patterns, a more complete computerized analysis is possible

The present method for studies of pulmonary mechanics demands a certain amount of basic technical resources and the method must therefore at present be reserved for the very large hospitals were equipment and personal staff are adequate It is felt that the costs of this type of investigations should not be grudged, since an efficient evaluation of the mechanical properties of the lungs will undoubtedly contribute to better prophylaxis and improved treatment of pulmonary disease of infancy

SUMMARY

For clinical studies of pulmonary mechanics in infants a new method is presented. This includes:

1) Measurements at sleep without use of sedatives.
2) Standardized measurements at rest and during carbon dioxide induced hyperventilation.
3) Carefully controlled equipment with respect to safety and comfort for the infants, avoidance of phase lag between the oesophageal pressure and air flow signals, and elimination of the effects of transient pressure variations in the ambient pressure.
4) Computerized calculations on line from the pressure and flow signals.
5) Possibilities of studies of the breathing pattern from e.g. pressure-flow loops.

With the method, normal infants were studied and normal values on e.g. tidal volume minute ventilation, dynamic compliance and "functional" pulmonary conductance are presented.

The method was found suitable for clinical routine studies of pulmonary mechanics during infancy even during severe ventilatory insufficiency. Two groups of infants were investigated: infants surviving severe neonatal respiratory insufficiency and infants with cardio-vascular left-to-right shunts.

The results from these studies indicate that the method can be used for diagnostic purposes, to obtain information of prognostic value and as a tool for evaluation of the effect of different therapeutical approaches to pulmonary diseases in infants.

ACKNOWLEDGEMENTS

I am deeply indebted to all friends at the Department of Clinical Physiology and Department of Pediatrics in Lund, who with their assistance and generous advice made this work possible. Financial support was given by the Medical Faculty University of Lund, the Swedish Medical Research Council (grant 14X 2872) and the Swedish National Association against Heart and Chest diseases.

REFERENCES

1. Ahlström H Jonson, B & Svenningsen, N W Continuous positive airway pressure with a face chamber in early treatment of idiopathic respiratory distress syndrome. *Acta Paediat Scand 62*433 1973
2. Bancalari, E Garcia, O L & Jesse M.J Effects of continuous negative pressure on lung mechanics in idiopathic respiratory distress syndrome. *Pediatrics 51*485 1973
3. Banerjee C.K., Girling, D.J Wigglesworth, J.S Pulmonary fibroplasia in newborn babies treated with oxygen and artifical ventilation. *Arch Dis Child, 47* 509 1972
4. Barnes, N D., Hull D Glover W.J & Milner A.D Effects of prolonged positive-pressure ventilation in infancy *Lancet II* 1096 1969
5. Blennow G. & Svenningsen N W Continuous positive airway pressure and noise level. *Lancet II*623 1973
6. Butler J., Caro, C G Alcala, R. & DuBois, A.B Physiological factors affecting airway resistance in normal subjects and in patients with obstructive respiratory disease *J Clin Invest 39* 584 1960
7. Chernick, V Heldrich, F & Avery M.E. Periodic breathing of p emature infants. *J Pediat, 64* 330 1964
8. Cook, C D., Sutherland J.M Segal, S Cherry R.B., Mead, J McIlroy M.B & Smith, C.A. *Studies of respiratory physiology in the newborn infant.*
   *III. Measurements of mechanics of respiration. J Clin Invest 36*440 1957
9. Doershuk, C F Downs, T D Matthews, L.W & Lough, M.D A method for ventilatory measurements in subjects 1 month–5 years of age Normal results and observations in disease *Pediat Res, 4* 165 1970
10. Bryan, M H. Hardie M.J Reilly B.J & Swyer P.R. Pulmonary function studies during the first year of life in infants recovering from respiratory distress syndrome *Pediatrics, 52* 169 1973
11. Fenner A. Schalk, U Hoenicke A Wendenburg, A. & Röhling, T Observations and studies of periodic breathing in premature and full-term infants *In* H. Bossart J M Cruz, A. Huber L.S Prod'hom and J Sistek (eds) *Perinatal medicine* 3rd Europ Congr Perinatal Med, Lausanne April 1972 p 336
12. Ferris, Jr B G & Pollard, D S Effect of deep and quiet breathing on pulmonary compliance in man. *J Clin Invest 39* 143 1960
13. Fry D.L. & Hyatt, R.E. A unified analysis of the relationship between pressure, volume and gasflow in the lungs of normal and diseased human subjects. *Am J Med, 29*672, 1960
14. Gregory G.A., Kitterman, J.A. Phibbs, R.H., Tooley W.H. & Hamilton, W.K. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure *New Engl J Med, 284* 1333 1971
15. Griffin, A.J., Ferrara, J D Lax O.J & Cassels, D E. Pulmonary compliance An index of cardiovascular status in infancy *Am J Dis Child, 123*89 1972.
16. Harrison V C., Heese H.V & Klein, N The significance of grunting in hyaline membrane disease. *Pediatrics 41*549 1968
17. Hotovy R., Enenkel, H.J., Gillissen, I., Jahn, U Keiser H. Kraft, H -G Müller-Calgan, H., Sommer S. & Wahlig, H. Zur Pharmakologie des 2-(4 -ter Butyl-2 6'-dimethyl-3 -hydroxybenzyl)-2-imidazoliniumchlorids. *Arzneimittelforschung, 11* 1016 1961
18. Howlett G Lung mechanics in normal infants and infants with congenital heart disease *A ch Dis Child, 47* 707 1972.
19. Hyatt, R.E. The interrelationships of pressure flow and volume during various respiratory maneuvers in normal and emphysematous subjects. *Am Rev Respir Dis, 83*676 1961
20. Jansson, L & Jonson, B A computerized method for studies of pulmonary mechanics at rest and during exercise Submitted for publication.
21. Jonson, B Pulmonary mechanics in patients with pulmonary disease studied with the flow regulator method. *Scand J Clin Lab Invest, 25* 363 1970
22. Karlberg, P., Cherry R.B Escardo F & Koch, G Respiratory studies in newborn infants I Apparatus and methods for studies of pulmonary ventilation and mechanics of breathing Principles of analysis in mechanics of breathing. *Acta Paediat Scand, 49* 345 1960
23. Krauss, A.N Tori, C.A., Brown J Soodalter J & Auld, P A.M Oxygen chemoreceptors in

low birth weight infants. *Pediat Res, 7*:569 1973
24 Krieger I. Studies on mechanics of respiration in infancy *Am J Dis Child 105* 439 1963
25 McIlroy M.B & Tomlinson, E.S The mechanics of breathing in newly born babies. *Thorax 10 58*, 1955
26 McNicol, K.N & Williams, H.B Spectrum of asthma in children — I, clinical and physiological components. *Brit Med J 4* 7 1973
27 Mikity V G & T ber P Complications in the treatment of respiratory distress syndrome bronchopulmonary dysplasia, oxygen toxicity and the Wilson-Mikity syndrome *Ped Clin N Amer 20*:419 1973
28. Milner A.D Assessment of respiratory function in neonates and infants. *I* Gairdner D. & Hull D (eds.) *Recent advances in Paediatrics*, London 1971 p. 231
29 N del, J.A. & Tierny D Effect of previous deep inspiration on airway resistance in man. *J Appl Physiol, 16*.717 1961
30 Nash, G Blennerhasset, J.B & Pontoppidan, H. Pulmonary lesions associated with oxygen therapy and artifical ventilation. *New Engl J Med, 276* 368 1967
31 Northway W H., Rosan, R.C & Porter D Y Pulmonary disease following respirator therapy of hyaline-membrane disease. *New Engl J Med, 276*.357 1967
32. Otis, A.B McKerrow C.B Bartlett, R.A., Mead J McIlroy M.B., Selverstone M.J & Radf rd E.P Jr Mechanical factors in distribution of pulmonary ventilati n. *J Appl Physiol, 8*:427 1956
33 Phelan, P D & Williams, H E. Ventilatory studies of healthy infants. *Pediat Res, 3*:425 1969
34 Polgar G Airway resistance in the newborn infant. *J Pediat 59* 915 1961
35 Polgar G Opposing forces to breathing in newborn infants. *Biol Neonat 11* 1 1967
36. Polgar G & Promadhat, V *Pulmonary function testing in children Techniques and standards* W B Saunders company Philadelphia, 1971
37 Prod'hom, L.S. The paediatrics aspects of f tal asphyxia The postasphyxia syndrome. *In* Huntingford, P.J Beard R.W., Hytten, F E. & Scopes J W (eds.) *Perinatal medicine*, London 1970 p. 131
38 Pusey V.A., Macphearson, R.J & Chernick, V Pulmonary fibroplasia following prolonged artificial ventilation of newborn inf nts. *Ca Med Ass J 100*:451 1969
39 Rasche R.F.H. & Kuhns, L.R. Histopathological changes in airway mucosa of infants after endotracheal intubation. *Pediatrics, 50*:632, 1972
40 Russel, G & Feather E.A Effects of feeding on respiratory mechanics of healthy newborn infants. *Arch Dis Chil, 45*.325 1970
41 Senterre J & Geubelle F Measurement of endoesophageal pressure in the newborns. *Biol Neonate, 16*:47 1970
42. Skoogh, B E. & Rizell S A high frequency response volume displacement body plethysmograph. *Scan J Clin Lab Invest, 31*:419 1973
43 Spoelstra, A.J G & Srikasibhandha, S Lung mechanics in infants recovering from respiratory distress syndrome *Biol Neonat 17*.321 1971
44 Stahlman, M. Long time results of respirator therapy *Biol Neonat, 16* 133 1970
45 Stern, L. The use and misuse of oxygen in the newborn infant. *Ped Cl N America, 20* 447 1973
46. Vert, P Andre M. & Sibout M Continuous positive airway pressure and hydrocephalus. *Lancet, II* 319 1973
47 Wallgren G Geubelle F & Koch, G Studies of th mechanics of breathing in children with congenital heart lesions. *Acta Paediat Scand, 49*:415 1960.
48 Wohl, M.E.B Stigol, L.C & Mead, J Resistance of the total respiratory system in healthy infants and infants with bronchiolitis. *Pediatrics, 43*:495 1969

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ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 245 1974

HEREDITARY NEPHROPATHY WITH HEARING LOSS "ALPORT'S SYNDROME"

BY ULLA MARIANNE IVERSEN

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

Contents

Acknowledgements

The author is grateful to Professor Martin Seip, Professor Ole Storstein, Dosent Erling Kluge Brodwall and Dosent Audun Flatmark, who have given valuable advice based on thei clinical experience of this disease.

Preface

During the last ten years hereditary nephropathy with hearing loss has been diagnosed with increasing frequency. This disease is characterized by haematuria, often combined with proteinuria, and can be aggravated by intercurrent diseases and by pregnancy. It is often combined with hearing loss of neurogenic type. In men the disease usually leads to an early death from uraemia, for women the prognosis is as a rule considerably better. It is possible that some cases of this hereditary disease are diagnosed as glomerulonephritis or pyelonephritis, which means that the disease is commoner than is generally supposed. It therefore seems important to make this hereditary nephropathy as widely known as possible.

April 1974

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Alport's syndrome

HISTORY

In 1902 Guthrie (4) in London described a family in which 12 of 15 members f two gene rations had 'idiopathic haematuria. All the pa tients had periods with increased haematuria, which was ften combined with fever malaise, headache, and pains in the back and legs. These periods could occur during infections such as the common cold, otitis, or influenza, or when the patients were exposed to extremes of temperature. Most of these patients also had proteinuria.

Later on the same family was examined by Kendall and Hertz in 1912 (56) and by Hurst in 1923 (48) some of the patients were by then dead from uraemia. It was then also noticed that three siblings, one sister and two brothers, were deaf

In 1927 the same family was described once more by Alport (2) and this time there was one more generation. Alport found that almost all those family members who had haematuria also had some degree of hearing loss, and it was he who first drew ttention to this combination as a special syndrome.

From 1929 to 1959 about 15 families with similar symptoms were described (13 35 38, 43 70, 75 82, 85 89 90, 94 103 106, 117) from many different countries. It was found that these families often contained members who were asymptomatic carriers of the trait, which started discussion on the hereditary aspects of this disease (38)

I 1961 W lliamson (118) described two more families and suggested the name Alport's syndrome for this disease. Tsilakos et al. (109) in Athens described two families in 1964 pointing out that the disease does not seem to be especi ally rare, and emphasizing that the often bad prognosis and the hereditary nature call for a very thorough examination of every case, including the family

During the last decade, up to 1972, about 150 more families were described in different parts of the world and of all races, whites, blacks, Asiatics. In the USA (1 3 6, 8, 15, 17 19 21 23 29 30 36, 37 47 49 51 55 58, 60 71 79 80, 83 91 98, 99 102, 104 114 115 116) Canada (9 70, 24 33 86, 108) South America (87), England (59 112), France (5 44 64 73 93), Belgium (46), Switzerland (26, 68, 88 97) Germany (25 31 32, 50 62, 97 100), Spain (69), the Netherlands (11 14) Denmark (45) Finland (81) Sweden (34 53 77), Japan (57 78), Ceylon (2_) Tasmania (119), and Israel (7 101)

SIGNS, SYMPTOMS AND COURSE

Kid ey signs and symptoms

On the whole, the clinical features do not differ much from those of glomerulonephritis or pyelonephritis. An acute or a chronic disease of one of these types is sometimes simulated. Some reports actually contain detailed discussions as to which of these diseases the individual patients were suffering from (18, 32, 55 87) In some patients nephrosis also appears (18, 43 44 58, 79 87 90)

The characteristic course in *a boy* is as follows. In connection with one of the infectious diseases of childhood or a common cold in early childhood or adolescence, he will suddenly begin to suffer from massive haematuria or headache or oedema of the face. The urine shows haema turia and/or proteinuria and often also cylindruria and leukocyturia. These urinary signs may in one and the same patient vary in degree dur

ing the following months, and in some patients they may almost disappear but they may become more pronounced again during the next infectious disease or after physical strain. There may be more or less pronounced hypertension In some persons the haematuria is less pronounced during the night or when they are at rest (70) Some have no haematuria at all but chronic or intermittent proteinuria (115) Most patients have both haematuria and proteinuria and even some cylinders of red blood cells. (Normal values are said to be less than 5000 erythrocytes per minute volume of urine (44)) (Cohen et al. (21) state the upper normal limit to be 3 erythrocytes and 5 leukocytes per vision field at high power microscopy) Signs of kidney insufficiency usually appear slowly after some years with slight oedemas, anaemia, increasing blood pressure and finally uraemia. Some boys have only a gradual onset of the disease. Most boys with this disease die from uraemia during adolescence. But there are some families (110) where the symptoms of kidney insufficiency do not appear until the age of 40–60 years.

In girls the course is usually more benign, and many women with the disease and with urinary signs similar to those of men can have many children and live to an advanced age. In other women with the same urinary signs, the disease can gradually or suddenly become aggravated, with symptoms of kidney insufficiency and they may die as children or in early adulthood (17 54 82, 106) According to Tischler et al (110) the disease takes a serious course in one or more girls in about 30–40% of these families. In some cases the symptoms alone or both symptoms and course are aggravated by pregnancy (20 79 115), although in some women there is only a temporary aggravation of the symptoms in connection with pregnancy (89) Chappell et al. (17) and Albert et al. (1) describe some families in which the prognosis for women is usually as bad as for men.

What is remarkable about this disease is that the symptoms vary so much in intensity in different patients and even within the same family and that the course can also vary from one family to another In the individual case, especially in women, it is very difficult to give a prognosis, at least in early stages of the disease The characteristic urinary signs of haematuria and/or proteinuria may be found in the children of these families as early as at birth (79) or in the first months or years of life (2, 3 13 32, 35 62, 70, 89 116) It is also said (110 116) that in these families there exist symptom free carriers of the trait, women as well as men.

Patients with Alport's syndrome are very susceptible to infections as children (85) They often suffer from angina tonsillaris, otitis media, chronic rhinitis, keratitis, and other contagious diseases, in connection with which the symptoms and signs from the kidneys may increase. The cause of this increased susceptibility is not known. In some cases, however a moderate hypogammaglobulinaemia during childhood has been noted (20, 75 and personal observation in 3 siblings) and in some cases changes in the beta lipoproteins (75) Some children with Alport's syndrome have periods with increased urinary changes even without concomitant infections. During these periods they may feel sick and suffer from fever slight apathy and sometimes pains in the abdomen or back (89)

Some children also suffer from nocturia, incontinence, or polyuria. There also seems to be a somewhat increased tendency to chronic or intermittent urinary tract infections (8 35 83) In these cases the differential diagnosis between Alport's syndrome and pyelonephritis can be difficult. Opitz (79) says that urinary tract infections in Alport's syndrome are commonest in women between 10 and 20 years of age. Of course the disease may in some cases really be combined with pyelonephritis (110).

In early stages of the disease, the concentration capacity of the kidneys seems not to be decreased and there are no changes in blood pressure or sedimentation rate, and no anaemia

In many cases the serum lipid values have been found to be normal although some patients have

high serum cholesterol without signs of nephrosis (15 20, 59 68, 104)

In acute and often also in chronic glomerulonephritis there are deposits of immunoglobulin in the glomerular mesangium (66 72). In Alport's syndrome, however there are no such deposits, either in the early or in the late stages of the disease (11 20, 54 55 104 111) Hoboith (45) has also examined some patients for autoantibodies against kidney tissue, with negative results. Serum complement is normal (104 113).

In some families high alpha-2-globulin fraction has been found in serum, higher than could be expected as a result of the slight nephrosis this sometimes even occurs without any sign of nephrosis at all (17 53 54 75 112, 118) Such an increase of a alpha -globulin may also be seen in other kidney diseases (23) and is not specific to Alport's syndrome.

Hearing loss

Sooner or later many of these patients develop hearing loss, which has been shown by audiometry to be of neurogenic type. It is most pronounced in men, but may also, usually to a lesser degree, be found in many women (82). Not all patients with Alport's syndrome have this symptom, and the frequency varies from family to family In some families hearing loss is not noticeable at all, even though some members on account of their urinary findings and for hereditary reasons, must be classified as having Alport's syndrome. Cassady et al. (15) found on examining some large families that about 60% of the men and about 40% of the women with this kidney disease also had neurogenic hearing loss. Some of the members of these families had hearing loss but no kidney disease, but they were carriers since they transferred the syndrome to their children

The hearing loss may start before the symptoms of the kidney disease appear It is often progressive, but usually stops after some years and most patients retain a certain hearing capacity The hearing loss is almost always bilateral, but is often of different degrees on the two sides. Usually it is the medium frequencies of the audiogram (1000–4000 freq/sec) that show an increased hearing threshold. The patient usually has difficulty in hearing an ordinary conversation, but can easily hear ery high and very low tunes. Cassady et al. consider that increasing hearing loss is often a prognostically bad sign for the kidney condition.

Changes in the eyes

In 1954 Reyersbach et al. (89) described a family in the USA in which many members had kidney disease and neurogenic hearing loss. Some of the members also had congenital anomalies of the eyes. The same year Sohar (103) also described a family in which Alport's syndrome was combined with anomalies of the eyes, mainly changes in the lens. The same complex of symptoms has later been reported by many authors (4 16, 26, 35 39 44 47 52, 67 75 84 90 106). In some families the nephropathy is combined with eye anomalies but not with hearing loss (97). The eye changes that are most often combined with Alport's syndrome are cataract, opacities in the lens, keratoconus, and severe myopia, sometimes combined with retinopathy (77) Cassady found that there was a significantly higher percentage of myopics among those with kidney disease than among normals in these families.

Changes in other organs

Goldbloom et al. (35) described 5-year-old boy who had Alport's syndrome combined with bilateral cryptorchism. I have seen two cases combined with bilateral inguinal hernia. Braun et al (10) and others (89 106) have described anomalies of the urinary tract. Different sorts of kidney anomalies may also be combined with this syndrome (98)

A few cases have been described with anomalies of the fingers or with spina bifida (8) and I have seen three cases with pectus excavatum.

Nervous symptoms

Marin et al. (65) report two cases of Alport's syndrome with neurological symptoms such as

tremor, myasthenia, decreased sensibility for vibrations and position, and decreased memory for recent events. In these cases the symptoms appeared during uraemic periods and they might therefore have been caused by the uraemia. However I have seen three siblings with Alport's syndrome who also had had slight, stationary neurological symptoms from early childhood, e.g. tremor, myasthenia, decreased sensibility in fingers and about the mouth, poor feeling of position and poor memory for recent events, but they all had very high intelligence. These symptoms had been observed for many years before signs of kidney insufficiency appeared. A family with similar neurological symptoms was seen by *Tenkhoff and Schriboer* (107). *Morin et al.* describe a family in which all and only those members suffering from haematuria had had one or more periods with short absences. These were often accompanied by pains in the stomach or seemed to be initiated by physical activity. The electroencephalograms were normal (70).

Many people with Alport's disease have been extremely thoroughly examined and all changes or anomalies noted. It is therefore possible that randomly distributed anomalies in the population have been noted in these patients because they have been examined especially thoroughly. Since these anomalies mentioned have only been noted in a few patients with Alport's syndrome, they may not be part of the syndrome.

Changes in amino acids

Some authors have described families in which Alport's syndrome was combined with an increase of one or more amino acids in blood and/or urine (24, 26, 32, 53, 77, 78, 97, 98, 112).

In other families a pure hyperprolinaemia has been found, often combined with a high excretion of proline, hydroxyproline, and glycine in the urine (26, 3., 36, 53, 59, 68, 69). Efron (28) describes such a family in which the hyperprolinaemia was shown to be caused by a lack of the enzyme proline oxydase. In some of the above-mentioned reports hyperprolinaemia or increase of other amino acids in the blood of some apparently healthy family members is also described (24, 26, 36, 59, 68, 98). In some of these families the hyperaminoacidaemia has been combined with late mental development, epileptic fits initiated by flashing lights and abnormal encephalograms (98), or with erythromelalgia and anomalies in the joints of the thumb (24) or with difficulties in articulation, choreoathetotic movements, lack of coordination of the upper extremities and weakness of the muscles with deviation of the spine, combined with normal intelligence, reflexes, and EEG (69).

Fig. 1. Histology of glomerulus from a 17 year-old male patient with Alport's syndrome and pronounced kidney insufficiency. Note periglomerular fibrosis and overall atrophy of glomerular tuft, though with some local epithelial proliferation. H & E. Initial magnification 1250 ×.

Many families with Alport's syndrome have normal values of amino acids in blood and urine (20).

PATHOLOGICAL ANATOMICAL PICTURE

Kidneys

Kidneys from *autopsy material* have mainly presented an uncharacteristic picture, with some features reminiscent of chronic glomerulonephritis, pyelonephritis, and interstitial nephritis (6, 9 16, 17 18, 22, 23, 35, 58, 60, 71 74 82, 87 90, 115 116).

Macroscopically the kidneys have been shrunken, with a pale granular surface, a thin cortex, and a diffuse border between the cortex and medulla. Usually the pelvis and ureters have been normal.

Microscopical examination has shown a varying amount of *glomeruli* to be hyalinized. Other glomeruli have had different degrees of changes with thick or splintered basement membrane, epithelial proliferation, crescent formation or adherences between the capillary loops and periglomerular fibrosis (Fig. 1) Balogh et al. (6) and Thibault et al. (108) have seen varying degrees of fatty deposits in some epithelial cells of the glomeruli Even in very shrunken kidneys some glomeruli can be normal microscopically in contrast to what is found in chronic glomerulonephritis. No leukocytes are seen in the glomeruli (60).

Some *tubuli* are atrophic, others are seen to be dilated with atrophic epithelium, and still others are lined by large, pale cells containing lipids (60, 87 115) (Fig. 2) Red blood cells are often seen in the tubuli.

Interstitially there is focal fibrosis with clusters of lymphocytes and in many cases also foam cells (35 82), especially on the border between cortex and marrow (Fig. 3) These foam cells are often arranged in rows between the tubuli, but they may also be grouped in irregular clusters. Krickstein et al. (60) have seen transition forms between lipoid-laden tubuli cells and interstitial foam cells and they assume that at least some of these foam cells represent degenerated tubuli cells. In some cases foam cells have been seen in the tubular lumen, and they may though rarely appear in the urine. Not all patients with Alport's syndrome have foam cells in their kidneys, and in families where Alport's syndrome is combined with aminoaciduria foam cells may or may not be seen in the kidneys (24 26, 59) The interstitial changes are thus unspecific and foam cells may also be found in other kidney diseases (96). It has been said, however that the number of foam cells is usually higher in Alport's syndrome than in other kidney diseases (60, 115)

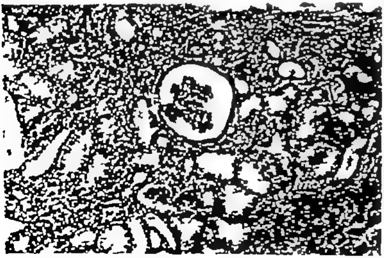

Fig 2. Section of the same kidney as shown in Fig. 1 showing increase of interstitial connective tissue, many lymphocytes and a mixture of dilated and atrophic tubuli. H & E. Initial magnification 210 ×

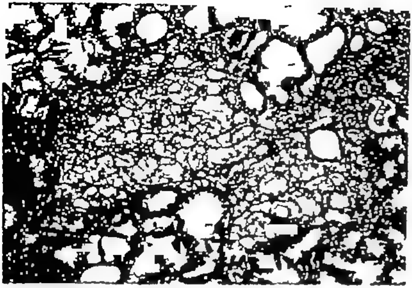

Fig 3 Section of the same kidney as shown in Figs. 1 and 2. Large clusters of foam cells are obvious. Hyaline cylinders in some tubuli. H & E. Initial magnification 400 ×

With the aid of different staining reactions Krickstein (60) has shown that the foam cells contain neutral fat, phospholipids, and cholesterol, but they seem not to contain mucopolysaccharides. This high content of cholesterol has been confirmed by later investigations (74). The origin of the fat that appears in the foam cells is not known.

Blood vessels Varying degrees of arteriosclerosis and arteriolosclerosis are seen in the kidneys. Other changes in the vessels are not reported

In *biopsy material* some erythrocytes in the tubuli and sometimes increased thickness of the basement membrane in the capillary tuft of the glomeruli have been found in the early stages of the disease (16, 60, 82)

Using the *electron microscopy* Rome et al (91) examined biopsies from 7 patients with more or less advanced Alport's syndrome and found a focally swollen basement membrane in the glomerular tuft, thick fused foot processes in the epithelial cells of the glomeruli, and small inclusions in the cytoplasm of the epithelial cells. These inclusions contain electron-dense granules, which might be lipid material. Similar findings have been made in other studies (3, 25). Rome et al. also found small ruptures in the basement membrane of the glomeruar tuft and think that this may explain the haematuria. The same changes are described by Kinoshita et al. (57) but they consider them to be unspecific, since similar changes may appear in glomerulonephritis.

At electron microscopy Chiricosta et al (20) and Hinglais et al. (44) found small dense particles, about 500 A in size, in the degenerated basement membrane in the gomerular capillaries in advanced cases of the disease. It is not certain whether these changes are pathognomonic for Alport's disease, but they have not been seen in glomerulonephritis. It is also not known whether they are to be found in the early stages of Alport's disease. Fusion of the foot processes in the glomerular capillary membrane and the appearance of small, dense granules are also described in cases of Gaucher's disease (12)

Lungs

Whalen et al (115) report one case where in the alveoli of the lungs they also found foam cells like those in the kidneys. I think it might be difficult to distinguish these from ordinary lipoid macrophages.

The ear

Crawfurd et al. (22) have examined the temporal bones from a boy who died from Alport's syndrome. They found atrophy of the organ of Corti and foam cells in the saccus endolymphaticus.

Similar changes have been found by others (5 39). Lackheim et al. (62) found collagen changes in the organ of Corti in some cases.

Peripheral nerves
In one case only (63) in a patient who developed polyneuritis symptoms, has a peripheral nerve been examined. Many macrophages resembling foam cells were seen between the nerve fibres and there was also atrophy of the myelin sheaths.

In those cases (two families) which have had Alport's syndrome and macrothrombocytopathy (29) small granules have been found by electron microscopy in the cytoplasm of the thrombocytes. These granules are very similar to those found by Hinglais (44) and Chiricosta (20) in the basement membrane of the glomerular tuft.

THEORIES ABOUT THE PATHOGENESIS

In the first reports of the disease Guthrie (42) supposed that it was caused by a *congenital weakness of the kidney vessels* leading to what he called 'renal haemophilia'. Later it was suspected (2, 27) that the disease was caused by an inherited *decreased resistance to streptococcus viridans*. This theory has been abandoned, however mainly because the immunoglobulin deposits in the glomeruli that are usually seen in the glomerulonephritis are not found in Alport's syndrome (11 44 55 104 113).

Some authors think that these patients have *a tendency to chronic urinary tract infection* and have found pathological anatomical changes in the kidneys resembling those in pyelonephritis. But against this theory of an infectious cause of the disease there is the fact that the earliest changes in Alport's disease seem to be localized only to the glomeruli. Furthermore, only some of the patients with Alport's syndrome have urinary tract infections (83), and these are mostly women (79), even though it is men who have the worst prognosis in this disease.

Van Buchem et al. (14) discuss whether the disease can be caused by a *congenital and hereditary anatomical defect in the distal part of the nephron*. At microdissection they found the distal part of the tubuli to be very atrophied. This was only found in one man, however who had died after a very protracted disease, and the changes may have been secondary to shrinkage and thus a sign of the final stage of the disease.

Some authors have thought, because of the haematuria, that it might be a *primary disease of the blood* with traits similar to haemophilia. None of the symptoms or signs, however support such a theory. No thorough electron microscopical or chemical studies of the different blood cells have been carried out. The disease does not seem to be linked to any special blood group (21).

Perkoff et al. (82) discuss whether the primary change is a *defect in lipid metabolism* with secondary changes in the kidneys and the cochlea. They point out the similar traits in Alport's and in Fabry's syndromes (angiokeratoma corporis diffusum universale), in which proteinuria and foam cells in different organs are found. This theory is supported by the fact that Neustein (74) and Krickstein (60) have shown that the fat in the foam cells is mainly cholesterol. Many of the patients with Alport's syndrome also have hypercholesterolaemia. On the other hand, many patients have normal cholesterol in the blood.

Goldbloom et al. (35) suspect an *inherited enzyme defect* with successive accumulation of a toxic substance. As already mentioned, Marin and Tyler (65) have demonstrated that there were foam cells in the kidneys as well as in the peripheral nerves in one patient with polyneuropathy complicating the hereditary nephropathy and other authors have found foam cells in the cochlea and the lungs, all of which indicates a widespread defect. Johnson et al. (49) mentioned the interesting fact that the kidneys, cochlea, and lens are attacked and discuss whether there is a gradual accumulation intercellularly of a toxic metabolite in the cochlea and lens.

This theory of a general metabolic defect has even received some support from McCrory et al. (23) and Kaufman (55). They suspect a meta

bolic or enzymatic *defect in the biosynthesis or metabolism of collagen*. A fact that lends support to this theory is that some patients with Alport's syndrome have congenital malformations or weakness of organs derived from fibrous tissue, such as skeletal malformations or bilateral hernia. Furthermore, in some families with Alport's syndrome there are pathological proline concentrations in the blood, and it is known that hydroxyproline constitutes about 14% of mammalian collagen. It is only in a few families, however, that Alport's syndrome has been combined with these changes in the amino acids and in other families the amino acids of blood and urine have been found to be normal. It cannot therefore be excluded that what has occurred here is the accidental appearance of two different diseases in these families. Against the theory of a defect in the metabolism of collagen there is also the fact that hyperprolinaemia and increased excretion of hydroxyproline can appear in other types of kidney insufficiency (95). On the other hand, in the families where Alport's syndrome is combined with amino acid changes, there are also members who show hyperprolinaemia but no kidney symptoms. Therefore, one might assume that there is some sort of connection between these two diseases.

Hinglais et al. (44), as mentioned, found in electron microscopical studies of kidneys from patients with Alport's syndrome that the glomerular basement membrane is focally or diffusely thickened fairly early in the disease. The membrane contains small, 500 Å inclusions. The authors suggest that it may be *a hereditary progressive degeneration of collagen tissue* with changes especially in the glomerular basement membrane, the cochlea, and the capsule of the lens. The collagen may be specific in these three places. Epstein et al. (29) studied under the electron microscope the thrombocytes in two families where Alport's syndrome was combined with thrombocytopathy and found small granules in the cytoplasm of the thrombocytes. Grøttum and Solum (41) found defects in the membranes of the thrombocytes in megacaryocytopathy. Epstein suspects that the nephropathy and megacaryocytopathy in these families are caused by one and the same abnormal gene. However, in one publication (40) in 7 patients with early Alport's syndrome with haematuria but with almost normal kidney function, the membrane of the glomerular tuft was found to be normal, without granules. This means that the granules seen in other, more advanced cases are a secondary phenomenon, perhaps accumulations of damaged organelles or of metabolites of abnormal collagen.

Further studies of collagen tissues from different parts of the body might help to explain the pathogenesis of this disease.

As Alport's syndrome seems to be caused by a dominant gene (see below) the symptoms appear in heterozygotes. In fact most cases of Alport's syndrome must be considered to be heterozygotes, which means that they have only one abnormal gene in this particular gene pair. Therefore it is not likely that the disease symptoms are caused by a general enzymatic defect, since enzymes usually, as stated by McKusik (61), have a high margin of safety, and symptoms from enzymatic defects usually only appear in homozygotes, where an enzymatic error is 100% expressed. Thus, most such diseases, depending on an enzymatic defect, are recessive.

In such a dominant disease as Alport's syndrome it seems more likely that there is an *error in part of a special structure protein*. My guess is *that there might well be a structural malformation* of all or a part of a special type of collagen in this disease, and that this collagen is mostly specific for the basement membrane of the glomerular tuft, for the cochlea and for the lens, but that it might also appear in small amounts in other collagen tissues. The different degrees of expression of Alport's syndrome in different individuals might be analogous to what is known from some other dominant diseases with incomplete manifestations. This abnormal or partly abnormal collagen might be more easily broken down than normal collagen or it

might produce toxic metabolities when broken down.

GENETIC STUDIES IN ALPORT's *SYNDROME*

Morphological chromosome studies have been carried out only in very few cases. In 1963 Gagnon et al. (33) described 5 patients who all had one extra chromosome in about 15% of their cells and a normal chromosome number in 85% of the cells. The trisomy was in group 19–20 However in this report the patients sex is not given and it is not made clear whether they in herited the disease from their fathers or mothers, the report is therefore of little value. The photographs of a cell with 47 chromosomes is from a woman, and cannot contribute to explain how the disease is inherited.

Lackheim et al (62) described a man with one extra chromosome in 12% of his cells on re peated examinations. The rest of his cells had a normal chromosome picture. The tissues from this patient, like the cells from Gagnon's pa tients, show a mosaic picture as to the chromosome number This patient had a daughter with normal chromosome picture, but with Alport's syndrome, which tends to refute the theory of a connection between morphological chromosome changes and the disease. Other authors (19 20, 71 77 80 91 97 98, 109 110) have found normal chromosome pictures in altogether 20 pa tients with Alport's syndrome and the patient described by Gagnon et al. was later examined by Pashayan et al. (80) who found a normal chromosome number There is thus little to in dicat a connection between the morphological chromosome changes and Alport's syndome However Royer et al (93) in their study of other congenital hereditary kidney diseases, found trisomy for chromosomes 18 or 13 or a deletion on chromosome III in some of these diseases. Therefore, it cannot be excluded that there may be chromosome changes in Alport's syndrome that are so small or that appear in such a small percentage f the cells that they are not observable by ordinary methods. The new Giemsa staining technique for examining the banding of the chromosomes may be helpful here.

Linkage tudies The locus of the gene defect is *not known* in those diseases that have been associated with Alport's syndrome, like macrothrombocytopathy lenticonus, neurogenic deaf ness, or hyperprolinaemia. It is therefore not *possible to find out with the help of these other* diseases in which chromosome the genetic change is localized. Sarre et al. (97) found that good many cases of Alport's syndrome belonged to blood group O but this has not been confirmed by other studies (21) It is not known whether there is any relation to a special lymphocyte phenotype.

Statistical hereditary studies It is difficult to understand how this disease is inherited, and during the last 20 years several theories have been proposed, founded on studies of large families in which the disease has appeared during several generations.

1 Stephens et al. (105) and Perkoff et al. (82) studied the same large family 122 persons were examined and of those 58 were healthy 50 had Alport's disease, and 14 were symptom-free carriers. From this the authors concluded that the disease was *dominant* and at least *partly sex linked* as it seemed to be inherited through women" Later on, however it was found that men with the disease can have healthy daughters and sick sons, which is not possible in a sex-linked disease, although it might be possible if crossing over occurred between the X and Y chromosomes. It is doubtful, however whether this can occur Bouchet et al. (13) put forward the theory that if the gene is located in the X chromosome or if it is partially sex-linked, this fact can explain why women have the disease so much less se verely than men in most cases, since then the other X in women might modify the disease.

Many authors doubt that partial sex linkage occurs in man. On the other hand, the so-called Lyon hypothesis (63) gives some support to the theory of partial sex-li kage in this disease Lyon is of the opinion that in female mammals only

one X is active in each cell so that every tissue in a female is a mosaic of cells as regards the active X chromosome. In some cells the X from the father is active, in other cells in the same tissue the X from the mother If Alport's syndrome were X linked, Lyon's hypothesis could explain why women usually have the disease less severely than men, since then the abnormal gene in women would not function in more than about 50% of the cells.

The fact that boys can inherit the disease from their fathers appears to refute the theory that the disease is X-linked Perkoff (83) suggests that boys who have inherited the disease from their fathers may have some chromosome abnormality of the Klinefelder type. There is, however no description of the Klinefelder syndrome in these patients.

Preus et al. (86) have examined several large families and they also doubt that the disease is X-linked, on the basis of the distribution of healthy and diseased children of fathers with the disease. These authors have made a very thorough statistical calculation covering three generations suffering from Alport's syndrome.

2. Graham (38) thinks that the gene is *autosomal dominant sex-influenced but not sex linked pleiotropic and incomplete penetrant* It is assumed to be incompletely penetrant because it does not give rise to symptoms in all carriers. As mentioned above, in families with Alport's syndrome there are now and then observed healthy men and women who transfer the disease to their children. It is also known that parents who suffer from the neurogenic deafness or the kidney disease alone can transfer both the deafness and the kidney disease.

Graham also thinks that some boys with the disease die in utero, which could explain why men with the disease have so many more healthy than diseased sons (83 86) Large statistical studies (110) have shown that fathers with the disease have totally (healthy + diseased) as many sons as daughters, and this fact contradicts the supposition that some boys die in utero. Tishler et al (110) have reported that fathers with the disease have more diseased than healthy daughters. This seems to disprove that the disease is autosomal.

3 Shaw et al (102) and Cohen et al (21) suspect that the disease is *autosomal and dominant* and that *non-random disjunction* often occurs. This means that in meiosis the abnormal gene more often goes to the oocyte than to the polar body in the first meiotic separation in women with the disease. This should explain why women with the disease have slightly more than 50% diseased daughters and sons. Shaw also suspect that the chromosome that carriers the abnormal gene is more usually associated with the X chromosome in meiosis in men *(preferential segregation)*

4 Arnott et al. (4) think that in addition to the abnormal gene there may be a modifying, X linked gene, but this hypothesis is rejected by Tishler et al. for statistical reasons.

5 Sarré et al (97) are somewhat critical of all the above-mentioned theories about heredity Even Preus et al. (86) say that there are still unsolved problems as regards the hereditary aspect of this disase, e g. why the disease is more serious in men despite its having a lower penetrance in men Tishler et al (110) have pointed out that the segregation ratios for the gene are unexpained, as least concerning inheritance through men. It is possible that Alport's syndrome with its different forms as regards men's survival time, is part of a larger complex of hereditary dominant kidney diseases that includes nephritis with erythromelalgia and nephritis with macrothrombocytopathy It is also possible that the disease is autosomal and dominant in some families, in other families sex linked, but studies of the different families are not yet extensive enough to solve this problem.

An observation which complicates the picture even more is that of Preus et al. (86) and of Grünfeld et al. (40), that men who inherit the disease from their fathers have it more mildly than men who inherit it from their mothers. They think this may be caused by unfavourable intrauterine conditions in diseased mothers, which

may increase the penetrance in those of their children who have the trait. I think Preus observation can also be explained by the fact that men who have inherited the disease from their f thers may belong to families in which the men usually have the disease more mildly and thus live longer so that they can have children. This has not yet, however been investigated.

The frequency of diseased children seems to rise in proportion to the age of the mothers with the disease (79), but there is not yet sufficient statistical evidence for this.

Bouchet et al. (13) believe than one gene is responsible for the nephropathy and one for the deafness, and that they are located near to each other on the same chromosome, but that they can be transmitted independently This is contradicted by the fact that a man who suffers from neurogenic deafness alone can transfer the kidney disease to his children Goldbloom also says that it is unlikely that two such unusual, independent symptoms would coincide as often as they do in this disease if they were not dependent on the same gene.

One may thus conclude that the genetic aspects of Alport s syndrome are not yet very clear It is not known on which chromosome the abnormal gene or genes are located or whether there is also a modifying factor involved. But it is likely that it is dominant, autosomal gene.

Further unanswered questions are (1) Why does the penetrance vary so much? (2) Why is the disease usually milder in women (3) Why is there fairly often a segregation between the kidney disease and the deafness? (4) Why is the penetrance so different in different families? (5) Why do diseased mothers often have more than 50% diseased children (6) Why is the disease milder in men who have inherited it through their fathers than in men who have inherited it through their mothers

PROGNOSIS AND CONSIDERATIONS OF TREATMENT

The hearing loss is usually not a very great problem, as it can usually be compensated quite well with modern hearing aids.

The most important clinical feature, and the one on which the treatment must be concentrated, is the *kidney insufficiency* Once begun it usually progresses to uraemia in a few years. Corticosteroids have no effect on the course (58) nor apparently has prolonged rest. The treatment of the progressive kidney insufficiency is the same as for other cases of chronic kidney insufficiency In recent years haemodialysis and transplantation have made the situation more optimistic.

A certain number of *transplantations* have already been carried out on patients with Alport s syndrome. The first attempt, as far as I know was made as early as 196.. (79) from a father to his son, who died soon afterwards. In the 9th Report of Human Renal Transplantation Registry 1972, (76) there are 83 transplantations recorded in patients with familial nephropathy Nothing is said about what type of familial nephropathy the patients suffered from, but one can assume that many of these are Alport patients. In any case, some successful transplantations to Alport patients are reported elsewhere (20, 29 34 60, 110) It is also said that patients with familial nephropathy have a somewhat better year survival than other patients with kidney transplantations (76) The explanation of this might be that patients with Alport s syndrome do not have the immunological complications that some glomerulonephritis patients have.

However Chiricosta et al. (20) discuss the possibility that even the transplanted kidney might be attacked by the disease if the disease is due to a metabolic defect. Hitherto the survival time of transplant patients has been too short to provide a solution to this problem. I think it unlikely that the new kidney would be attacked, since it seems to me to be most probable that it is not an enzymatic metabolic defect but an error in the organ structure that causes Alport s syndrome.

There are special problem with regard to transplantations for Alport patients, since for

genetic reasons it is rather difficult to have a living *donor* from the family However this problem can be solved by using necro-kidneys, as is becoming more and more common.

Another very important problem is *genetic counselling* The patient may not be aware that his disease is hereditary or he may think that the trait has disappeared when he receives a new healthy kidney The patient has a right to known and to be informed that the disease is hereditary and to have explained to him the consequences of this. As a general rule one can say that women with the disease or with the trait all run the risk of having about 50% of their sons and 50% of their daugthers diseased or carrying the trait. Men with Alport s disease also run the risk of having about 50% of their daughters diseased or carrying the trait, but only 12% of their sons.

Another ethical question is how much *prognostic and genetic information the other family members* ought to have. The prognosis for those with kidney insufficiency is not completely bad, since they now have the possibility of kidney transplantation. Not all survive the operation, however and it is as yet unknown how many years the new kidney will function. If the trait becomes more widespread among the popula tion, because many now survive a transplantation and have more possibilities to reproduce, it might even become an economic problem. With the high risk of having diseased offspring with all the psychological burden this will impose on the children, most affected parents might renounce the idea of having children. Even if they could choose to have only girls, this would only transfer the same sad problems to the next generation.

It is especially important to inform those women who have the disease mildly that the risk of their having affected offspring is as high as the risk for those more severely diseased. The same percentage risk is also valid for carriers.

On the other hand, the symptom free members of these families should not renounce the idea of having children, since there is a very small risk that they have the trait.

The young patient with Alport s disease may also need some guidance as to his choice of oc cupation. A profession which demands the exer cise of physical strength should be avoided, and the deafness must also be taken into consideration.

Abstract

Alport' syndrome is a familial kidney disease which is transmitted in approximately the sam way as an autosomal dominant trait It is usually transmitted through mothers who have the diseas but sometimes through fath rs and very seldom also through symptom-f e carriers, both men and women, in these families.

The symptoms usually appear during hild hood and re macroscopical and microscopical haematuria, proteinuria cylindruria and leukocyturia, all of arying intensity and sometimes intermittent Th disease usually has a more severe course in men, who usually die of uraemia between the ages of 15 and 30 ears The dis ease is usually combi ed with neurogenic hearing loss which appears at about 10 ears of age is somewhat more common in men, and progresses parallel to the kidney disease Deafness may also appear in famil members wh have no sign of the kidney disease but who can transmit either or both symptoms In som families Alport s syndrome is combined with myopia or other anomalies of the eyes, in some families with aminoacid ria, in some with skeletal abnormalities, and in some with eurological disturbances or psychiatri symptoms

All children with nexplained renal haematuria ought t hav an audiometric examination and their parents and siblings should have thorough urine and audiometric examinations All children with neurogenic hearing loss ought to hav thei urin xamined and th rest of the family should have an audiometric and urin examination.

References

1. Albert, M. S., Leeming, J M., Wigger H. J Familial nephritis associated with the nephrotic syndrome. Am J Dis Child 117 153 1969
2. Alport, A. C. Hereditary familial congenital haemorrhagic nephritis. Brit M J 1.504, 1927
3. Antonovych, T T., Deasy P F., Tina, L. U., D'Albora, J B., Hollerman, C. E., Calcagno, P L. Hereditary nephritis: early clinical, functional and morphological studies. Pediatr Res 3:545, 1969
4. Arnott, E. J Crawford, M D A., Toghill, P J Anterior lenticonus and Alport's syndrome. Br J Opthal 50:390 1966.
5. Babai, F Bettez, P Lésions oculaires du syndrome d'Alport. Ann Anat Pathol (Paris) 13 289 1968.
6. Balogh Jr K., Gloor F Nierenveränderungen bei der erblichen Nephropathie mit Innenohrschwerhörigkeit. Verh Dtsch Ges Pathol 49 Tagung:200, 1965
7. Ben-Ishay D., Biram, S., Ullmann, T D Familial nephritis. Isr J Med Sci 3:106, 1967
8. Berlyne, G M. Familial nephritis. Manch Med Gaz 41.26, 1962.
9. Bettez, P Babai, F Lésions rénales du syndrome d'Alport. Ann Anat Pathol (Paris) 13.277 1968.
10. Braun, F C., Bayer J F Familial nephrosis associated with deafness and congenital urinary tract anomalies in siblings. J Pediatr 60:33, 1962.
11. Brentjens, J R. H., Feltkamp-Vroom, T M., Tiddens, H. A.W M., Kuyten, R H. Localization of plasma proteins in kidneys of children with diffuse nephropathies, studied by an indirect immunofluorescent technique Acta Paediat Scand 58.374 1969
12. DeBrito, T Dos Reis, V G Penna, D O., Camargo, M. E. Glomerular involvement in Gaucher Disease. Arch Pathol 95 1 1973
13. Bouchet, M Paquelin, Syndrome familial de néphropathie avec surdité. Ann Otolaryngol Chir Cervicofac 73 895 1956
14. van Buchem, F S. P Beetstra, H Hereditary renal disease associated with deafness Alport syndrome. Acta Med Scand 179 319 1966.
15. Cassady G Brown, K., Cohen, M., DeMaria, W Hereditary renal dysfunction and deafness. Pediatrics 35:967 1965
16. Castleman, B., Kibbee, B. U Case 43511 case records of the Massachusetts General Hospital. New Engl. J Med 257 1231 1957
17. Chappell, J A., Kelsey W M., Winston-Salem, N C. Hereditary nephritis. Am J Dis Child 99:401 1960.
18. Chaptal, J Jean, R., Pages, A., Bonnet, H. Néphropathie hématurique familiale avec surdité (Syndrome d'Alport) Pédiatrie 20:649 1965
19. Chazan, J A., Zacks, J Cohen, J J Garella, S. Hereditary nephritis. Am J Med 50:764, 1971
20. Chiricosta, A., Jindal, S. L., Metuzals, J Koch, B Hereditary nephropathy with hematuria (Alport's Syndrome). Can Med Assoc J 102.396, 1970.
21. Cohen, M. M., Cassady G Hanna, B L. A genetic study of hereditary renal dysfunction with associated nerve deafness. Am J Hum Genet 13:379 1961
22. Crawford, M D'A., Toghill, P J Alport's syndrome of hereditary nephritis and deafness. Q J Med 37:563, 1968.
23. McCrory W W Shibuya, M Worthen, H G Hereditary renal glomerular disease in infancy and childhood. Adv Pediatr 14 253, 1966.
24. Cross, E. G The familial occurrence of erythromelalgia and nephritis. Can Med Assoc J 87:1 1962.
25. David, H., Grossmann, F Marx, I Natusch, R. Elektronenmikroskopische Befunde an der Niere beim Alport-Syndrom. Frankf Z Pathol 76:12, 1966.
26. Dubach, U C., Minder F C., Antener I Familial nephropathy and deafness: First observation of a family and close relatives in Switzerland. Helv Med Acta 33.36, 1966.
27. Eason, J Malcolm Smith, G L. Hereditary and familial nephritis. Lancet 2:639 1924.
28. Efron, M. L Familial hyperprolinemia. Report of a second case associated with congenital renal malformations, hereditary hematuria and mild mental retardation with demonstration of

an enzyme defect. New Engl. J Med 272:1243, 1965.

29. Epstein, Ch. J., Sahud, M. A., Piel, C. F., Goodman, J. R., Bernfield, M. R., Kushner, J. H., Albin, A. R.: Hereditary macrothrombocytopathia, nephritis and deafness. Am J Med 52: 299, 1972.

30. Farber, S., Vawter, G. F.: Clinical pathological conference, The Children's Hospital, Boston. J Pediatr 68: 661, 1966.

31. Friedburg, D.: Pseudoneuritis und Drusenpapille beim Alport. Klin Monatsbl Augenheilkd 152: 379, 1968.

32. Fuhrmann, W.: Das Syndrom der erblichen Nephropathie mit Innenohrschwerhörigkeit (Alport-Syndrom). Dtsch Med Wochenschr 88:525, 1963.

33. Gagnon, J., Archambault, L., Ducharme, J. R., Katyk-Longtin, N.: Résultats préliminaires sur une étude cytogénétique d'une famille affectée de néphropathie. Rev Can Biol 22: 133, 1963.

34. Gisetson, N., Lindberg, L. G., Lindholm, K.: Ärftliga njursjukdomar i patientmaterial från Njurkliniken i Lund. Nord Med 85:783, 1971.

35. Goldbloom, R. B., Fraser, F. C., Waugh, D., Aronovitch, M., Wiglesworth, F. W.: Hereditary renal disease associated with nerve deafness and ocular lesions. Pediatrics 20:241, 1957.

36. Goyer, R. A., Reynolds, J., Burke, J., Burkholder, P.: Hereditary Renal Disease with neurosensory hearing loss, prolinuria and ichtyosis. Am J Med Sci 256:166, 1968.

37. Grace, S. G., Suki, W. N., Spjut, H. J., Eknoyan, G., Martinez-Maldonado, M.: Hereditary nephritis in the Negro. Arch Intern Med 125:451, 1970.

38. Graham, J. B.: Hereditary chronic kidney disease: An alternative to partial sex-linkage in the Utah Kindred. Am J Hum Genet 11:333, 1959.

39. *Gregg, J. B., Becker, S. F.: Concomitant progressive deafness, chronic nephritis, and ocular lens disease. Arch Ophtalmol 69: 293, 1963.*

40. Grunfeld, J.-P., Bois, E. P., Hinglais, N.: Progressive and nonprogressive herditary chronic nephritis. Kidney Internat 4:216, 1973.

41. Grottum, K. A., Solum, N. O.: Congenital thrombocytopenia with giant platelets; a defect in platelet membrane. Br J Haematol 16:277, 1969.

42. Guthrie, L. G.: Idiopathic or congenital, hereditary and family haematuria. Lancet 1:1243, 1902.

43. Hamburger, J., Crosnier, J., Lissac, J., Naffah, J.: Sur un syndrome familial de néphropathie avec surdité. J Urol Nephrol (Paris) 62:113, 1956.

44. Hinglais, N., Grünfeld, J.-P., Bois, E.: Characteristic ultrastructural lesion of the glomerular basement membrane in progressive hereditary nephritis (Alport's syndrome). Lab Invest 27: 473, 1972.

45. Hobolth, N.: Nephropathia Hereditaria (Alport syndrom). Nord Med 71:345, 1964.

46. Hooft, C., vanHacker, K., Nerbeeck, J.: Hematurie familiale. Acta paediat Belg 17:201, 1963.

47. Howe, H. G., Smythe, C. M.: Hereditary nephropathy associated with nerve deafness and ocular lesions. Clin Res 10:43, 1962.

48. Hurst, A. F.: Hereditary familial congenital haemorrhagic nephritis occurring in sixteen individuals in three generations. Guy's Hosp Rep 73:368, 1923.

49. Johnson, W. J., Hagan, P. J.: Hereditary nephropathy and loss of hearing. Ann Otolaryngol Chir Cervicofac 82:166, 1965.

50. Jost, L., Schleche, M., Weigl, E.: Das Syndrom familiärer erblicher Nephropathie mit Innenohrschwerhörigkeit (Alport Syndrom). Med Welt 40: 2340, 1967.

51. Joshi, V. V.: Pathology of hereditary nephritis. J Clin Pathol 21: 744, 1968.

52. Junod, J. P.: La néphropathie héréditaire avec surdité et atteinte oculaire. Actualités Néphrologiques Hôpital Necker. Paris, Flammarion, 1963, p. 79.

53. Karlberg, B.: Alport' Syndrome. Report of Cases at Medicinska Riksstammen, Stockholm, 1968.

54. Kaufman, D. B., McIntosh, R. M., Smith, F. G., Vernier, R. L.: Diffuse familial nephropathy: A clinicopathological study. J Pediatr 77:37, 1970.

55. Kaufman, D. B.: Familial nephropathy. Am Heart J 82: 839, 1971.

56. *Kendall, G., Hertz, A. F.: Hereditary familial* congenital hemorrhagic nephritis. Guys Hosp Rep 66:137, 191..

57. Kinoshita, Y., Osawa, G., Morita, T., Kobayashi, N., Wada, J., Ebe, T., Watanabe, H., Murohashi, K., Murayama, M.: Hereditary chronic nephritis (Alport) complicated by nephrotic syndrome. Acta Med Biol (Niigata) 17:101, 1969.

58. Knepshield, J. H., Roberts, Ph. L., Davis, Ch. J., Moser, R. H.: Hereditary chronic nephritis complicated by nephrotic syndrome. Arch Intern Med 122: 156, 1968.

59. Kopelman, H., Asatoor, A. M., Milne, M. D.: Hyperprolinaemia and hereditary nephritis. Lancet 1075, 1964.

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200. Dean M., Cravioto, Joaquin, Ramsden, Lydia and van Veen, Astrid, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. 1970
201. Sutherland, Lynette E., Herrick, Phyllis, Iuda, John U., Bailey John D. and Lynch, Matthew J., Barrett's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatus and Glomeruli. 1970
202. Fomon, Samuel J., Filer Jr, L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. 1970
203. Åkerberg, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. 1970
204. Berg, Kristina, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Matti Dahl. 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Child-psychiatric and Electro-encephalographic Study on Primary School Children in Umeå. 1970
210. Rosberg, Georg, *Parental Attitudes to Pediatric Hospital Admission.* 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. 1971
212. Helmfors, Alpo, Urinary Excretion of Vanillylmandelic Acid of Children in Normal and Certain Pathological Conditions. 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. 1971
214. Samuelson, Gösta, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. 1971
215. Bengtsson, Sheila Margaret, *A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped Children.* 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. 1971
217. *Pediatric Work Physiology, Proceedings of the Karolinska Institute Symposium.* Stockholm, August 30–September 1, 1970. Edited by Claes Thorén. 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. 1971
219. Judd, Doris, Hartwell, Stanley, Manning, Mary and Kate, Graciela, Coronary Arteries in Newborn Children. Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. 1971
220. Hellman, Niels, Bäckström, Leena, Kantero, Riitta-Liisa and Tiisala, Rauno, Studies on Growth of Finnish Children from Birth to Ten Years. 1971
221. Bohman, Michael, A Comparative Study of Adopted Children, Foster Children and Children in Their Biological Environment Born after Undesired Pregnancies. 1971
222. Johansson, Erkki, Plasma Magnesium Levels during the First Five Days of Life. 1971
223. Fomon, Samuel J., Thomas, Lora N., Filer, Jr., L. J., Ziegler, Ekhard E., and Leonard-Michael T., Food Consumption and Growth *of Normal Infants Fed Milk-based Formulas.* 1971
224. Klackenberg, Gunnar, A Prospective Longitudinal Study of Children. Data on Psychic Health and Development up to 8 Years of Age. 1971
225. Sundberg, Pekka, Physical Growth of Children with Congenital Heart Disease. Pre- and Postoperative Study of 115 Cases. 1971
226. Hagberg, Bengt, Sanner, Gunnar, and Steen, Monica, The Dysequilibrium *Syndrome in Cerebral Palsy. Clinical Aspects and* Treatment. 1972
227. Antila, Riikka, Renal Involvement in Juvenile Rheumatoid Arthritis. A Clinical and Histopathological Study. 1972
228. Hilmanen, Pentti, Wendelin, Helfrid, Lindberg, Ossian, and Fogelius, Märten, Chronic Respiratory Paralysis. A Clinical Study of 12 Patients in Long-term Respirator Treatment after Poliomyelitis. 1972
229. Bosse, Giovanni, Gyulemardit, Antonio, Sorignani, Pier Giorgio, Mandelli, Michele, Franco-Bossi, Silvano, and with statistical collaboration of Fantoni, Lodovico, The Systemic Systolic Blood Pressure of Newborns with Low Weight. A Multiple Regression Analysis. 1972
230. Aaltonen, Elina, Late Prognosis of Children Born into Tuberculous Households. The Effect of Isolation and Simultaneous BCG-vaccination. 1972
231. Sandlund Junker, Karin, Selective Attention in Infants and Consecutive Communicative Behavior. 1972
232. Hagne, Ingrid, Development of the EEG in Normal Infants During the First Year of Life. A Longitudinal Study. 1972
233. Wendelin, Helfrid, Microangiography of the Liver. An Experimental Study of Sheep from the Prenatal to the Fullgrown Period. 1972
234. Gerrard, J. W., MacKenzie, J. W. A., Goluboff, N., Garson, J. Z., and Maningas, C. S., Cow's Milk Allergy: Prevalence and Manifestations in an Unselected Series of Newborns. 1973
235. Köhler, Lennart, Health Control of Four Year-Old Children. An Epidemiological Study of Child Health. 1973
236. *Proceedings of the Seventeenth Nordic Paediatric Congress.* Reykjavík, June 27–June 30, 1973. Edited by Peter Johan Moe. 1973
237. Sillanpää, Matti, Medico-Social Prognosis of Children with Epilepsy. *Epidemiological* Study and Analysis of 245 Patients. 1973
238. Nilsson, Jürgen, von Willebrand's Disease in Sweden. 1973
239. Persson, Harriet, The Finnish Skolt Lapp Children. A Child Psychiatric Study. 1973
240. *Rearing of Non-identical Twins with Lymphogenic Hypogammaglobulinaemia under Gnotobiotic Conditions.* Edited by W. M. Teller. 1973
241. Salmi, Toivo T., Haptoglobin Levels in the Plasma of Newborn Infants, with Special Reference to Infections. 1973
242. Valimäki, Tapio, Analyses of Serial Echocardiograms in Healthy Newborn Infants During the First Week of Life. A Comparative Study by One- and Two-dimensional Echocardiography. 1973
243. Lundström, Nils-Rune, Clinical applications of echocardiography in infants and children. 1974
244. Ahlström, Hans, Studies on Pulmonary Mechanics in Infants. 1974
245. Iverson, Ulla, Hereditary Nephropathy with Hearing Loss "Alport's Syndrome". 1974

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ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 246 1974

TRAINING OF MEDICAL AND DENTAL STUDENTS IN MENTAL RETARDATION

BY JAKOB ØSTER

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

TRAINING OF MEDICAL AND DENTAL STUDENTS IN MENTAL RETARDATION

To the Parents of the Mentally Handicapped

ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 46 1974

From the Department of Paediatrics (Head: Jakob Øster, M.D.)
Centralsygehuset, Randers, Denmark

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This work was carried out
under the auspices of the International
League of Societies for the Mentally Handicapped

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"suit the action to the word
the word to the action"
(Hamlet, Act 3 Scene)

INTRODUCTION

During the past 20–30 years the medical and dental professions have shown increasing interest in the problems concerned with mental retardation (4 12 13 18) As a result of this it has been repeatedly asserted from various sources that general practitioners and paediatricians have a responsibility to these children and adults and their parents (6 14 25 27) Parents associations have been particularly responsible for expressions such as these but attention has also been drawn to these conditions from the medical profession itself (16 19) It is no secret that parents of mentally retarded children are not always satisfied with the insight and the efforts made by the medical profession in this field and they have therefore to an increasing extent suggested or even demanded that doctors should increase their knowledge of mental retardation during their pre and post graduate education in order to alter their intentions and improve their efforts if they desire to continue to accept the responsibility for the diagnosis therapy and counsel in this important but apparently difficult field (16)

The International League of Societies for the Mentally Handicapped in 1971 selected the topic Training of Medical and Dental Students in Mental Retardation for consideration and I was asked to work with the project

Primarily we formed a committee with interested people from many parts of the world Among these Irving Stone from California performed the investigation in that area, Donald Beasley from New Zealand did the same in that country and in Australia. Bertil Hall from Sweden collected the Swedish material while I undertook the collection of the material from the other Scandinavian countries and Finland.

The present work is the conglomerate of literature studies, studies and considerations from the collected material and the results from discussions with people who are experienced in mental retardation and/or medical education.

But the main task remains namely the further consideration and adaptation of the ideas stated This must be made by the reader who is responsible for the training of medical and/or dental students by those who are experienced in general medical education and by the people who are responsible for the economic basis of medical training and probably are obliged to give priority to some topics and coordinate the use of the available resources

The welfare of the retarded and the happiness of their families depend on the decisions made by these people

LITERATURE ON THE TRAINING OF MEDICAL AND DENTAL STUDENTS IN MENTAL RETARDATION

The literature on the topic is rather sparse

Whitney (31) in 1945 was probably one of the first to mention how mental retardation might be presented to medical students In 1953 Bradley (3) as the first documented a definite programme of medical education in

mental retardation which had been in operation in the medical school at the University of Oregon since 1948 as a part of the activities of the Department of Pediatrics He stresses that practical rather than theoretical aspects must be the focus of attention if you want to interest the students as potential family doctors The programme was designed to reach also pediatric residents practising physicians and nurses

Herman Yannet (34) medical director of the Southbury Training School Connecticut and at the same time associate clinical professor of pediatrics at Yale Medical School in 1957 describes a pediatric intern and resident training programme integrated with a training school for the mentally retarded The article is preceded by the following statement by the contributing editor of Pediatrics Grover F Powers The ultimate solution of the manifold problems of mental retardation will come through research It seems obvious that the practical way to promote investigation is to affiliate some fashion universities and institutions for the care of the mentally retarded persons

Yannet assumes that there has always been a shortage of qualified professional personnel in the field of mental retardation but this need has recently been multiplied due to the stimulation created by the parents organizations and the growing public faith that research may solve the problems of prevention and due to the fact that funds have been available for research

The training of physicians in the field of mental retardation involves (1) diagnosis of mental retardation etc (2) understanding of special education etc (3) experience in associated fields like epilepsy c.p etc Most of the postgraduate training sources will continuously be superficial and imperfect The new training system will give experience based on a competently supervised training in comprehensive diagnostic and guidance centers developed in connection with hospitals or medical schools and the well organized and medically staffed Training Schools for the retarded There must be geographical proximity between the two institutions and the medical standard and equipment at the Training School must be good Furthermore there must be a research programme—or at least a constant spirit of medical curiosity

This exchange programme between Southbury Training School and the Department of Pediatrics at Yale University Medical School started in 1945 Gradually it included interns as well as residents The interns spend 7 weeks and the residents 6 months and at present about 100 physicians have participated the programme prepared for them having been designed primarily as a part of their pediatric training

The programme has raised the medical standard at the training school and it has helped to increase the interest and knowledge of a gradually expanding group of physicians who may be expected to become potential key figures in developing community interest and participation in meeting the over-all problem of the retarded"

From the same year (1957) there is an article on professional education and mental retardation by Grover F Powers (28) He mentions the increasing interest in mental retardation increasing congress-activities and the *increasing offers of funds for research* and emphasizes the so called parents movement as the incentive of all this He says that 'the physician of the future must be qualified to deal with the chronic disabilities and diseases which at both ends of life s spectrum are increasing in incidence *According to him the greatest part* of the m r education for physicians must be placed in the postgraduate training.

The primary purpose of the parents associations was to promote and stimulate research personnel-training and recruitment This is the same goal which the American

National Association for Retarded Children had in 1950

Powers described enthusiastically the affiliation systems mentioned by Yannet, between educational institutions and residential schools for the mentally retarded as one of the best ways for the physician who wants to learn something in the field of mental retardation provided that there is a research programme

He knows that the medical student in his pregraduate training learns about mental retardation in his pediatric training and that some students work in day care centers. The essential thing which the student has to learn is "that mental retardation is one of the great areas of humanitarian and educational concern and that its impingements are extensive in many scientific directions He advocates the cooperation between medical schools and training schools with undergraduate clinical clerkships graduate residences and symposia. The same can be done not only within the medical profession but also for psychologists educators and others He concludes that our urgent lacks are interested top-flight investigators and teachers more good teachers to train more students to develop more teachers to train better students

At the first international medical conference on mental retardation in Portland Maine in 1959 George E. Gardner (7) gave an account of his view on mental retardation as part of the training programme in child psychiatry According to him all physicians should during their medical school education become acquainted with certain basic facts in regard to this childhood disability—through didactive lectures clinical demonstrations and clinical work and through pediatric internship and residency training He suggests that somewhere in the curriculum a more detailed coverage of this field is necessary Clinical work can be done in neurological pediatric or mental retardation clinics or in collaboration between the clinics

He is aware that isolated placement of the training schools may be a hindrance Finally he asks for better communication and fellowship between the two specialties because I feel that the problems of child development constitute our single and we hope someday unified body of knowledge"

Co-operative programmes of training and research in mental retardation are mentioned in detail by Darrell A Hindman (10) at the London conference in 1960 (1962) The programmes are very different and the best ones are those where the plans are constantly being revised and altered Most of the programmes are concerned with education and some fewer with psychology and medicine For the success of the programme an outstanding leadership excellent personal relationship and adequate communication are essential The wealth and variety of clinical material is most important And so are scientific reputation and the establishment of consultancies and joint-staff appointments whereas distance and isolation can be overcome

In 1963 Hilda Knobloch (15) tells about a conference on teaching mental retardation in medical education, that was held in Columbus Ohio in September 1957 and mentions among the participants Charles Bradley Richard L. Masland Grover F Powers Jack Rubinstein George Tarjan, Herman Yannet and Rick Heber

According to Knobloch "the major focus of responsibilities will be shared by pediatrics psychiatry and neurology· it would seem essential that psychiatry refocuses attention on the intellectual disorders and a greater liaison with departments of pediatrics is needed Three levels of education are mentioned (1) The undergraduate medical student will learn to recognize moderate deviations and interprete them. He must learn those techniques and attitudes essential to patients with chronic disabilities (?) The postgraduate education of the intern and resident (3) The specialist in mental subnormality

Medical school training in mental subnormality is not likely to be expanded and enriched until faculties have on them persons with an interest in and background of knowledge and experience in neuro-psychiatric disabilities of childhood. The past few years have seen an incredible change in the extent to which problems of mental subnormality are being included and considered in medical school curricula.

Diagnostic clinics have been erected and cooperation has started between institutions for the mentally retarded and universities, but medical schools will not send students, interns and residents to institutions which are not supervised by well-qualified staff.

At the Vienna congress in 1961 P. C. Benton (2) gives an account of a graduate training programme in mental retardation for professional personnel. In 1957 the Oklahoma Mental Retardation Training Center started, located at the Children's Medical Center of Tulsa, which had an established multi-disciplinary programme for handicapped children with a staff consisting of pediatricians, child psychiatrist, neurologist, public health nurse, social worker, psychologist, child development specialist, speech therapist, nutritionist, occupational therapist and a physiotherapist! They perform several and varied courses, where a 2 week course is especially popular.

At the Copenhagen congress on the scientific study of mental retardation in 1964 Cecil C. Wittson (32) told about advantages and problems of a university clinical research center for mental retardation, and at the Montpellier congress in 1967 she did the same in collaboration with Robert B. Kugel. The clinical research center for mental retardation of the Nebraska Psychiatric Institute was established in 1961 and has in many respects been a prototype of the ten regional research centers in mental retardation requested by late president John F. Kennedy February 5, 1963. Its objective is to provide facility for scientific work and to provide a setting for teaching and training of pertinent disciplines at the undergraduate, graduate and postgraduate level. The Nebraska center includes a 10 bed research ward with the most modern equipment and a staff of some 75 interdisciplinary professionals and with some 79 different unidisciplinary and interdisciplinary projects in progress (1964).

Wittson & Kugel (33) stress that the goal for such Medical College programmes is teaching, research and service! The student shall be given insight into and be confronted with some of *the great problems* he will meet as a doctor. Mental retardation is one of them! Through this training the student will also learn much about society.

In 1966 Donald J. Stedman (29) explains his thoughts concerning the training of physicians in mental retardation as viewed by a psychologist at Duke University Medical Center. He has 2 years' experience in bringing behavioral skills and psychological principles to the training pediatrician and the pediatric staff. He mentions as some goals of the programme (1) to make the trainees see the broad scope of mental retardation, (2) to familiarize the M.D. with the diagnosis and management technique available for the retarded, (3) to teach him the responsibility for working with a family and (4) to provide him with a knowledge of the roles of other professionals working with the retarded. The group has been working at four levels of teaching. (1) First medical school class, (2) Third and fourth year medical student rotating through pediatrics, (3) The pediatric resident and (4) The practicing pediatrician. The latter was the most eager student and he is considered by Stedman to be "the key stone or fixed point of referral or the traffic cop" for the continuum of care that has to be developed for each child that is mentally retarded.

At the Montpellier congress 1967 Samuel Giammona (8) told about the university affiliated facility programme for the mentally

retarded in Miami Florida which will give service training and research based primarily on a vigorous department of pediatrics a strong division of special education, and an expanding psychology department The facility will establish a multidisciplinary programme for service training and research

In Mental Retardation Construction Programme from the U.S Dept of Health Education and Welfare Washington D C 1971 (22) a survey of the 30 university affiliated facilities in the U.S is presented At present (1973) we are expecting to hear of the preliminary results of all these efforts which are of importance for the training of professional personnel at different levels of education

In 1971 there was a Scandinavian symposium in Oslo on dentistry for handicapped people where Svatun (30) from Norway delivered a paper on "A programme for the teaching of dental students in the field of handicapped children He gives a good description of the contents of lectures seminars and supervised working with patients At the same symposium the Danish dentist Sv Aage Andersen (1) gave an account of his experience in the teaching of dental students in the problems of mentally retarded patients It seems that dentists are rather interested and active in all fields of handicapping conditions including mental retardation Cfr among the references people like Brown & Warren (4) Jago (1 13) Massler (19) and Olsen (23)

Recently Pilkington (?6) while describing new audio-visual teaching techniques suggested that the main focus for the future doctor should be a social pattern rather than a clinical one in the field of mental retardation.

Last but not least Holt & Huntley (11) predicted that the growing medical interest in mental retardation, stimulated by the recent advances in cytogenetics and biochemistry might be linked with an increasing awareness of the community and its need by the medical profession. Based on their investigation from Britain they emphasized an increasing demand for training in mental retardation at an under and postgraduate level This seems to be the first work aiming at examining and documenting what really is done and what is required based as it is on interviews with 105 doctors and questionnaires received from ?0 out of Britain s 31 medical schools.

The conclusion drawn from the literature is that the greatest contribution to the training of medical students in mental retardation seems to be the affiliated systems of the U.S including pediatric intern- and residents training programmes with emphasis on service training and research (21)

Geographical proximity between the medical school and the mental retardation institution seems to be important But still more important is a high medical standard at the mental retardation institution and some sort of research programme

The responsibility for the future teaching programmes must be shared by pediatricians psychiatrists and neurologists—with emphasis on social psychological and educational aspects

The general practitioner and the practicing pediatrician may be the keystone for the referral of care for the mentally retarded child

Furthermore there seems to be a great interest in mental retardation and other handicapping conditions from the odontological field of science and practice especially from Australia, Denmark and Norway

The background for the common demand for improving training seems to come from the parents organisations and from the epoch making discoveries in disciplines such as cytogenetics and biochemistry

PROCEDURE AND MATERIAL

After some preliminary correspondance with people who might be interested in the project in different countries and who were experts in mental retardation and/or medical education it was decided to get information from the responsible chairmen within various medical and dental disciplines at the medical schools and dental highschools of different countries i e most often the professor(s) of the discipline

In advance we had decided to give the priority to the training of medical students and only secondarily the dental students We also wanted to concentrate on pregraduate training, but secondly we would try to consider postgraduate training of physicians We would give priority to mental retardation (m r) but also if it was possible consider training in other handicapping conditions (o h c.) without specifying the topic Furthermore we would attempt to obtain information from students and from young physicians who recently graduated and who now were working in hospital or in general practice to hear their opinion concerning the training in mental retardation which was offered to them during their studies we wanted to know how and where they got the most valuable training, and in which fields they thought the training ought to be supplemented according to their new experience

In Denmark Finland Norway and Sweden we used the following questionnaire which also in a somewhat changed form was used in New Zealand and Australia, and in California

---

Parents of mentally retarded children often claim that physicians knowledge of the problems of mental retardation is too limited—and physician now and then emphasize that during their studies they had too limited training in mental retardation and other handicapping conditions and their social consequences.

The International League of Societies for the Mentally Retarded has formed a committee to make world-wide survey on "Training of the medical and dental students in the field of mental retardation

As a chairman f thi committee I apply to you as co-responsible for the clinical pregraduate training of medical/dental students [illegible] in the subject of Pediatrics/Psychiatry/Child Psychiatry/Social- and Community Medicine/Dentistry

W would be glad to know *how many lessons* (45 minutes each or 60 minutes each) were given to the student during his entire clinical education in

A mental retardation

B other handicapping conditions.

How was this time distributed among:

		A	B
I	General principles		
II	Test-proced res		
III	Early diagnosis		
IV	Different clinical types		
V	Clinical cytogenetics		
VI	Inborn errors of metabolism		
VII.	Genetic counselling		
VIII	Care & nursing & general medicine		
IX.	Social and psychological implications		
X	Treatment		
XI	Helping programmes and legislation		
XII.	Parents problems		
XIII	Other (specified)		

How was the time distributed mong:

(*a*) Lectures ______
(*b*) Symposia ______
(*c*) Clinical demonstrations ______
(*d*) Visits in institutions ______
(*e*) Work in clinics or outpatient-cli ics ______
(*f*) Otherwise—which ______

Who gave the training and instruction.

(1) Professors ______
(2) Lecturers ______
(3) Assistants or others—who? ______

Which *textbooks* do you use
or advise
Do the *students follow* these lessons.
Do the students cut these lesson s:
Why do you feel?
Do you use a *well-planned* programme
Do you use *occasional* lessons only

What is your experience with *postgraduate training* [illegible] the two subjects A and B?

Do yo know of any *chair in oligophrenology?*
Would you consider this appropriate?
Do you feel that *oligophrenology should be a separate medical specialty*

Furthermore we would be glad if yo would *supply any personal information* on both subjects.
personal onsiderations,
suggestions and recommendations for further research and another viz. better training in mental retardation and other handicapping conditions within your specialty or other specialities.

Yours

Table 1 *The numbers of teachers in different disciplines from Scandinavian countries who responded or did not respond to the questionnaire*

	Denmark		Finland		Norway		Sweden		Total	
	Answer	No answer	Answer	No answer	Answer	No answer	Answer	No answer	Answer	No answer
Pediatrics	5	0		1		0	7		16	1
Psychiatry	3	3		1	3	0	7		[illegible]	4
Child psychiatry		0	[illegible]		0	–			4	0
Soc./general medicine		0		0	4	0	1		9	0
Odontology		[illegible]	1	1		0	0		5	1
Genetics	1						–		1	0
Oligophrenology	1	1		–		–	–		1	1
Total	*16*	4	*7*	3	*11*	0	*17*		*51*	7

Such an international undertaking as the present investigation inevitably runs into great and unforeseen troubles For this reason the Scandinavian material seems to be the one from which the most extensive conclusions may be drawn It will therefore be mentioned first and afterwards the results from California and New Zealand Australia.

In Denmark we have three universities in Finland there are three in Norway two and in Sweden six They all have medical schools and some of them like Copenhagen Lund have several rather independent medical schools

We received replies from 51 specialists who all are responsible or co-responsible for the training of medical and dental students in their different disciplines and thus also responsible for the amount of training in mental retardation

From Table 1 one can learn that 46 physicians and 5 dentists replied and one may notice how the respondents and the non-respondents were distributed among the different medical disciplines Only one pediatrician did not reply From Sweden we did not obtain the total number of teachers which had been asked for It is evident that the interest for the problem is very intense in all the disciplines mentioned which probably are the only ones in which mental retardation is treated to any extent. The problems of other handicapping conditions may well be dealt with in disciplines such as physiotherapy orthopedics etc —but only the disciplines stated in the table were investigated

We also asked ten young general practitioners 5 who graduated from Copenhagen and 5 who graduated from Århus University and furthermore 10 interns from the same universities about their opinion as to the problems of mental retardation relating to teaching and training We received replies from 6 practitioners and 5 interns

RESULTS

In the following the results taken from the questionnaires will be presented As much as possible has been put into tables but a great deal more has to be given as quotations or statements which have special importance and consequence because they have been given by leading and responsible professionals from different medical disciplines Inevitably there will occur some overlapping of topics.

Table 2 *Number of hours spent on mental retardation (m.r) and other handicapping conditions (o.h c) in different disciplines*

	Pediatrics		Psychiatry		Child Psychiatry		Soc./general med.		Odontology		Total	
Number of hours	m r	o.h c.	m.	o.h.c	m.r	o h c	m.r	o.h.c	m.r	o h c	m.r	o.h.c.
Some	1	1		1	1	0	2	0	1	0	7	
–5	3	4	6	0	3	0	3	1		0	17	5
6–10	8	5		0	0	0	1	0	1	0	12	5
11–15	1	0		0	0	0	0	0	0	0	3	0
16–20		1	1		0	0	0	0	0	1	3	4
1 30	0		0	0	0	0	1	0	1	0		
With information	15	13	13	3	4	0	7	1	5	1	44	18
No information	1	3		1	0	4		8	0	4	5	31
Total	16	16	15	15	4	4	9	9	5	5	49	49

NUMBER OF HOURS FOR M R AND O H C

Table 2 shows how many hours were spent with teaching in mental retardation (m r) and other handicapping conditions (o h c) within the different disciplines during the pregraduate education In most disciplines they gave less than 10 hours Eight used re than 10 hours on m r and six more than 10 hours on o h c In some few cases the number of hours is not stated only some hours The majority of the disciplines only devoted 2–5 hours for this training 17 in m r and 5 in o h c Pediatrics probably use most time and thereafter psychiatry and child psychiatry And soc./ general medicine seems to use a little less time an exception being the institute of Åbo Finland which uses 30 lectures for each field

Concerning o h c it is practically only the pediatricians who give information

A few hours may be used for a well-planned course of course On the other hand it is repeatedly pointed out that the curriculum is so sparse that m r and o h c can only be covered with a few hours, especially in psychiatry and child psychiatry The pediatricians often state that both fields are part and an important part of the general pediatric training and the total time where m.r and o h.c have been touched is impossible to tell One pediatrician says

> During the last terms of their pregraduate clinical studies the students have a clinical lecture twice a week, including clinical demonstration and examination. This means about 25–30 lectures in pediatrics in each of the last three terms
>
> A great part of the teaching is devoted to oligophrenia and different handicaps like c.p. sense defects, aphasia, other motoric and physical handicaps too much, in the opinion of some

Another says that he never loses a chance to lecture on care and service on parents problems etc Also the pediatricians bed side-teaching can hardly be estimated but this form of training probably is very important because the students here make a personal and direct contact with the mentally retarded child and his parents

The pediatric clinic of Århus seems to be a place where many hours are spent about 20 for m r and about 30 for o.h c And again it is from this clinic pointed out that as far as I can judge m.r and o.h c are mentioned in about 50 of the 150 lessons

The psychiatric clinic of the same university seems to have a short but well planned course in m r given by a lecturer with great personal and practical experience in this field

Also the pediatric university clinic of Oulu Finland has an extensive programme

Table 3 *The distribution of the mentioned themes in the pediatric (ped) vs. psychiatric (psych) clinics*

	Ped.	Psych
A Early diagnosis	8	5
B Clinical syndromes	7	9
C Care and treatment	5	9
D Parent problem and information	4	3
E Social aspect and resources	5	5
F Cytogenetics	6	3
G Genetical counselling	7	3

Results of the symposium concerning training of medical students i m made during the second spring-term 1971 in Swedish university-clinics: 7 for child psychiatry 1 for *psychiatry 8 for pediatrics, and 6 for social medicine*

T Total number of clinics

N Number of clinics with planned programme in m

I Number of clinics with visits to institutions for m

A Average number of lessons

	T	N	I	A
Child psychiatry	7	3		2 40 minutes
Psychiatry	1	9	8	5 40 minutes
Pediatrics	8	8	6	4 40 minutes
Social medicine	6	0		

covering 17 hours for m r and 30 hours for o h c and well-planned in cooperation with the institute of social and general medicine

The Dental Highschool of Bergen Norway uses 21 hours on m.r and 18 hours on o.h c but not timely concentrated or limited to one special department

The programme from the psychiatric clinic of Gothenburg also seems to be well-planned and extensive the course is made by the psychiatrist in collaboration with the geneticist

As a transition to the mentioning of various aspects of m r the following may be inserted here

In Sweden Dr Bertil Hall and Dr Sture Rayner undertook an investigation in 1971 concerning the training of medical students in mental retardation A questionnaire was circulated and in the fall of 1971 the work was carried out and the result can be summarized in the following way as to the various disciplines

Social medicine (comprising 6 university institutes)

At one university the teaching had not been started In another they cover m r in 6 lessons provided they have patients for demonstration In a third place they are accustomed to training in m.r —but had skipped it in the last term due to special circumstances Both the last-mentioned two clinics usually made a 2–3 hours visit to an institution for mentally retarded In the other three institutes for social medicine they had no fixed lessons on m r

Child psychiatry (7 university clinics)

In three clinics m r was taught in the form of lectures (2×40 minutes) Besides the A B C D and E-aspects (see Table 3) they have mentioned different forms of educational training. From two clinics they had arranged a visit (one resp two hours) to an institution for m r

Psychiatry (13 university clinics)

In one clinic the training had not been started In nine other clinics they have a training-programme in mental retardation In two of these they give 10 lectures (40 minutes each) In one clinic 6 lectures In three clinics 4 lectures And in further three only 2 lectures In eight clinics they visit (2–7 hours duration) institutions for mentally retarded

Pediatrics (8 university clinics)

One clinic did not answer In the other seven clinics the training consists of 1–8 lectures (4 at an average) each 40 minutes. In five clinics they make a visit to a m.r institution of 1– hours duration

Concerning the subjects which have been taught in the different disciplines the following can be stated

Social medicine No fixed lessons for m.r

Child psychiatry In no clinic did they teach for more than 2×40 minutes In the three clinics which trained the students in

m.r the aspects A B C D and F were covered

Pediatrics In six out of the seven clinics they have mentioned early diagnosis (A) different clinical types (B) cyto-genetics and genetics (F and G) A little less interest concerning care (C) information (D) and helping programmes of the community (E) As a curiosity it may be mentioned that in one clinic they covered aspects A B D F and G in 1 hour and in another clinic the aspects A C E and F in 8 hours

Psychiatry All nine clinics have given lectures on B and C. D F and G have been covered in three clinics and A and E were covered by five clinics Furthermore aspects like epidemiology and testing procedures were mentioned

Pediatrics and Psychiatry Altogether lecturing was carried out in 16 clinics. The aspects which were most neglected were information and helping programmes of the community which had been given proper consideration in only six and nine clinics respectively

THE COVERING OF DIFFERENT ASPECTS OF M R

It has been difficult not to say impossible to use the statements concerning the different aspects (I–XIII) which were covered by the teaching Yet the perusal leaves the impression that most aspects are covered by the pediatricians while the psychiatrists generally are reluctant to give any statement on this point. Furthermore we can add the following supplementary statements

From Denmark a professor in pediatrics says that he pays great attention to the students evaluation of the child s intellectual development from thorough anamnesis and through clinical judgement Sometimes the psychologists demonstrate their testing procedures All points I–XIII in the questionnaire are treated The students are offered an opportunity to work at the out patient department for handicapped but only a few accept this offer We have not been able to visit institutions for m r

Another one offers a general description.

> Aspects which in this way often are mentioned are early diagnosis genetic counselling, general medical care helping programmes legislation parents problems—and different clinical types.
>
> About 7 regular hours are spent with m.r and 5 with other handicapping conditions. At first the themes in question are general principles, inborn errors of metabolism cyto-genetics, testing procedures, and social and psychological aspects.

A third pediatrician from Denmark gives a broad description of how the problems of m.r are integrated in the general training in pediatrics

> During the fourth clinical term the students have 25 lectures (45 minutes each) in pediatrics. 1 hour is devoted to general principles of oligophrenology 1+1 hours about inborn errors and chromosomal abnormalities. 1 hour concerning c p Furthermore the student are informed of mental retardation when we are mentioning hypothyreosis, perinatal damage etc.
>
> During the fifth clinical term small groups of students are attached to pediatric department for one month and they get about 20 lessons including 1 hour with mental retardation 1 hour with c p 1 for metabolic and chromosomal aberrations. At the same time the students get bedside-teaching including m r and other handicapping conditions according to the patient available at a given time.
>
> During the 6th and 7th term the students have about 25 clinical lectures, and I would guess that 10% of this training is concerned with the fields in question.
>
> We have not been able to arrange visits to institutions or special outpatient clinics, but during the weeks the students spend in the children s hospital they participate also in the outpatient clinic and with cases of m and other handicaps also of course

At the Royal *Dental* Highschool of Copenhagen the institute for pedodontia gives 2–4 lessons divided between general principles and various clinical types Furthermore the students have access to independent observation or treatment of mentally retarded and otherwise handicapped children

The pediatric professor from the University of Århus gives the following description with comments on mental retardation mentioning the number of lessons and the various aspects

Mental retardation can be regarded from several points of view: pediatric, psychological, psychiatric and social aspects—as suggested from the questionnaire. Other handicapping conditions cover great deal of ll pediatric diseases like .p chronic joint disease diabetes melitus, asthma, haemophilia etc. And as such they occupy much time in the curriculum.

The curriculum in pediatrics is 90 hours, spread over 5th, 6th, and 7th clinical term—and furthermore one month course at the 4th term when the student get about 40 formal hours teaching, i. total of 130 hours teaching. And according to my judgement mental retardation and other handicapping conditions are mentioned in about 50 of these lessons. The various aspects cannot be separated as to time. Many of these topics are dealt with in other disciplines like genetics, psychiatry hygiene and social medicine

In Helsinki the greatest importance seems to be attached to various clinical forms and clinical cyto-genetics The distribution over the other aspects is quite even except for general medical care and nursing, to which they do not seem to pay any attention.

The *pediatric* clinic of the University of Oulu has made the agreement with the Institute of *social and general medicine* that the training of medical students in the field of mental retardation and other handicapping conditions is carried out during the students training in general pediatrics

M r is covered by about 17 hours and other handicapping conditions by about 30 hours. In the first discipline much importance is attached to testing procedures parents problems and the various clinical types. In the second field early diagnosis various clinical types social aspects and helping programmes are given the priority

Furthermore there is an account on the training in m r from the pediatric clinic of Malmö as follows

(1) A clinical conference (2 hours) with the cooperation of a pediatrician who is trained in handicaps, and physicians working with the mentally retarded W have 3 patients for demonstration, and w give survey concerning etiology in m early diagnostic methods, helping programmes, educational forms, and other social measures.

(2) During lectures on c.p and convulsions, m is mentioned

(3) During lectures and clinical demonstrations some cases with Dow syndrome and other cases of m.r are show At the same time the difficulties in early diagnosis, estimation of development, and parent problems are discussed

(4) Two hours are devoted to lectures on genetic counselling.

(5) Finally some problems are discussed concerning etiology during lectures on inborn errors of metabolism and endocrine disorders. Sometimes lso urts were arranged to institutions for mentally retarded. At present this is impossible because the courses have been reduced to tw weeks.

According to my point of iew it would be difficult to xtend the training in m.r with the present curriculum. But this, of course doesn't hinder further planning or more intensified training.

From a Danish psychiatrist we have the following statement

The present curriculum for psychiatry too limited with the result that the training in m.r hitherto has been quite insufficient.

During the formal lectures in psychiatry 3 lectures are given, on an average concerning oligophrenia, including survey of the various clinical types, symptomatology social and psychological spects etc For several years w visited an institution for mentally retarded but for the last tw years thi had been given up due to lack of reimbursement for the teaching persons.

And from the *psychiatric* research center at St Jörgens Hospital Gotehburg, you have the following:

A an answer to the inquiry distributed I like to gi the following data on how the training of medical students in mental retardation is arranged during the courses given at my institute

I give tw hours on general principles and epidemiology then four hours clinical cyto-genetics the last tw of these four also including other psychiatric defect than mental retardation.

The students are then taken for two full days cursion to different institutions and hospitals for the mentally retarded. I think I can say that during those tw day all items in the formula under A are covered I lecture on those items in the bus, and meetings are arranged between students and personnel of different kinds. The visit includes special schools, wards, pecial institutions for epileptics and special schools for slightly mentally retarded patient with complicated behaviour All lectures and demonstrations in th field are given by me personally that II professor

THE FORM OF TRAINING

The training most often is given as traditional lectures as can be read from Table 4 Clinical demonstrations are also frequently used whereas symposia do not seem to be

the result seems to be a well-planned programme with 17 hours for mental retardation and 30 hours for other handicapping conditions

Furthermore the Finnish pediatricians must spend 6 months at an institution for mental retardation during their training to become a specialist So the pediatricians have great experience in this work.

In *Norway* the Dental Highschool has like dental highschools in other places a well-planned programme and it seems better than in most medical schools where you often find from the statements that one discipline doesn t know what the other ones are doing. The lack of communication and coordination seems to be outspoken in several countries

Sweden seems to have a really well planned programme at St Jörgens psychiatric hospital Gothenburg due to the professor s enthusiasm and personal interest in mental retardation Otherwise the programmes in Sweden seem according to the teachers to be limited but planned

THE INTEREST OF THE STUDENTS

Thirty-two teachers inform us that the students are interested in the topics mentioned in 17 cases no answer was given But nobody says that the students were uninterested and avoided this training One teacher mentions that the students were offered an opportunity to work at the outpatient department for handicapped 'but only a few accepted this offer probably due to lack of time

Another Danish pediatrician mentions that about 15–50% of the students attend the training in m r and other handicapping conditions the same percentage as in other teaching

A Danish teacher in legal and social medicine feels that the students are interested but that the access to training in the field is by and large non-existing She means that the students organisations have arranged visits to institutions for m.r and these visits are well visited and popular

One young Danish intern admits that he did not follow the lessons on m r etc. because there was no demand for examination in the field!

All Finnish students seem to be interested one psychiatric teacher says admirably ! The same is true for Norway where a dental institute arranges visit to institution for m r during the students sparetime— and this visit is well attended the students are very interested

In Sweden all students seem to attend all lectures

OLIGOPHRENOLOGY AS AN INDEPENDENT SPECIALTY AND CONSIDERATIONS ON A CHAIR IN OLIGOPHRENOLOGY

These two topics are often treated simultaneously by the responding teachers

A Danish pediatrician says

> Maybe we must accept it (m.r) as a specialty but due to its integration in several disciplines I would prefer that the problems of mental retardation also in the future are taught in the old-fashioned way in the pregraduate training of the students.

Another Danish pediatrician argues against oligophrenology as an independent specialty and he is also against a chair

As you can learn from Table 8 most teachers did not respond to the question and from the respondents the majority (15) said No and only four one pediatrician and three psychiatrists said Yes

From Table 9 you will learn that most teachers did not respond to the problem of a chair in m r But 17 said No and 9 Yes And you may notice that especially the psychiatrists were in favour of a chair whereas the pediatricians are against it One Swedish pediatrician says pediatric oligophrenology belongs to the pediatric neurological section as the diagnosis mainly

Table 8 *Should oligophrenology be an independent specialty?*

	Pediatrics	Psychiatry	Child Psychiatry	Soc./general Medicine	Odontology	Total
Yes	1	3	0	0	0	4
No	6	3	1	2	3	15
No information	6	7		6	2	23
Do not know	3		1	1	[illegible]	7
Total	16	15	4	9	5	49

concerns patients less than ? years of age A Danish pediatrician says No—because m.r according to my view is a very essential part of pediatrics and another one feels that "the resources could possibly be better used A third favours a chair and is of the opinion that this specialty should be a subspecialty under pediatrics

A child psychiatrist says that it

> depends on how the teaching and research in this field might be integrated with psychiatry child psychiatry and pediatrics, and on the existence of qualified research workers And another one does not give much credit to chair in oligophrenology I believe that the cross-professional character of the discipline can be retained And the same I feel concerning oligophrenology as an independent specialty I the short view it might increase the prestige of the discipline but I think that we shall abandon further subspecialization and encourage the versatile aspects where no specialty as such stands lone

On the other hand we have a suggestion from a Danish psychiatrist for an independent chair in oligophrenology with the following addition especially if it could be pointed out that the discipline has a further aim than the medical faculty Other psychiatrists also have been active for a chair but in vain.

In contrast to the Odense team from Denmark which is not in favour of oligophrenology as an independent specialty or a chair you will find from Table 7 that 4 out of 6 general practitioners and 1 out of 4 interns feels that m r ought to be an independent specialty and furthermore that 4 vs 2 advocate a chair They feel that these innovations might give a better training in this field which they practically all feel has been neglected in their academic education One of them adds, however that the condition of this new specialty must be that the specialist moves outside the institution and watch the children in their own environments

From the institute of social medicine in Oslo the responsible teachers have repeatedly tried to indicate the need of a chair in oligophrenology at the medical faculty in Oslo because the field is being neglected by all the relevant instances at any event the psychiatric ones But it seems difficult to find the place for this post within the setting of a medical faculty

Table 9 *Would a chai in oligophrenology be appropriate*

	Pediatric	Psychiatry	Child Psychiatry	Soc./general Medicine	Odontology	Total
Yes	1	5	1	1	1	9
No	7	3	1	3	3	17
No information	6	6		5	1	20
Do not know	2	1	0	0	0	3
Total	16	15	4	9	5	49

Table 10 *Postgraduate experience*

	Yes	No	No information	Total
Pediatric	8	1	7	16
Psychiatry		2	11	15
Child Psychiatry		1	1	4
Soc./general medicine	0	3	[illegible]	9
Odontology	3	1	1	5
Total	15	8	26	49

EXPERIENCE IN POSTGRADUATE TRAINING

From Table 10 you can see that several pedatricians have some experience in this field—often with cytogenetics or genetic counselling—and because such training is a part of the programme for pediatric neurology or for the training in specialties like pediatrics and child psychiatry In Finland 3–6 months work at an institution for m r is included within postgraduate training in pediatrics and the experience from this arrangement is good and the pediatricians have great experience in this work

The Danish general practitioners and interns felt that many of us have obtained knowledge by postgraduate training and one of the interns finds that a post graduate training in m r would be considered desirable for all physicians who get into contact with the problem and this would be more appropriate than an enlargement of the field in the pregraduate medical training

This is a very important statement

From the odontological institute of Helsinki we find the same opinion: It seems likely that the training and the dental treatment of the m r will mainly be included in the postgraduate training. And furthermore a Swedish pediatrician says A more comprehensive intrusion in the problems of m r belongs to the postgraduate training in pediatrics and child psychiatry

Several other teachers have suggestions for more and better postgraduate training: A Danish dentist finds that a systematic postgraduate dental education should be established concerning the handicapped child as well as the adult patient and from Sweden we have the suggestion that 'the postgraduate training in pediatrics should contain a period of regular care under supervision for mentally retarded children

CONSIDERATIONS SUGGESTIONS AND RECOMMENDATIONS FOR FUTURE IMPROVEMENT

From the questionnaires you can find much criticism of the present state of things and many suggestions for improvements of the future training of medical students in m.r

A young Danish teacher in social medicine says

You are surprised when you look back on your clinical training and try to count the lessons where you were taught of m.r or other handicapping conditions.

I the discipline social medicine there are lect res on legal aspects et of m.r

I discipline psychiatry the general principles of m.r are dealt with in one lecture.

Furthermore you may come upon patient with Down s yndrome or microcephalia etc. in pediatrics and medicine but t is only occasional

The students organisations e.g IMCC have arranged on their own initiative visit to the institutions for the mentally retarded These arrangements are well attended by the students who want to learn about oligophrenology through the medical superintendents and others who in their daily work occupied with these special problems and who want to observe the mentally retarded in the special environment of these institutions.

I feel that the students are interested but that the access to training in the field is by and large nonexisting.

Concerning the first teacher's comment. "The clinical problems are referred to psychiatry of course." I can state that during my stay for practical work in the psychiatric department which is compulsory in the curriculum, most students observed a sharp division between oligophrenic and psychotic patients—and the former are not admitted to the psychiatric department unless they are also psychotic Consequently the students are not trained in oligophrenology and the problems of these patients at all And for the same reason you will not see oligophrenic patients demonstrated in psychiatric lectures.

I would find it reasonable that the students ought to spend some time, e.g. two weeks, at an institution for the mentally retarded—just as it is compulsory with stay at psychiatric unit—at least until well-planned training in the field of mental retardation has been arranged.

From a Danish child psychiatrist you have the suggestion for an extension of the curriculum—and for a training across the specialties with a coordination in the form of symposia in collaboration with pediatrics and social medicine—and here oligophrenology should also be dealt with But this belongs to the future !

The statement has the following considerations regarding the future

During recent years the sharp limit between different disciplines are moving within the medical discipline there has been an increasing interest in the etiology and treatment of the handicapped and at the same time enlargement of the practical work of the social system All this means that it is less appropriate to stick t old concepts in this field

Oligophrenology is cross-professional discipline—and the teacher should train not only medical students but also other groups like psychologists, dentist etc

As one of the child-psychiatrists who has had much contact with m problems and cooperation with the Services for the mentally retarded due to my work with psychotic children I have a strong feeling that our training of the students in that field is inadequate and so is the knowledge and capability of the physician in general This also holds true for child-psychiatrist and I always stimulate intending doctors to supplement their education by an appointment at an institution for the mentally retarded because no theoretical education can compensate for personal experience But it is not "m at present In the training course for intending child psychiatrists, one day is devoted to oligophrenology

In the training of student I would suggest an extension of the curriculum—need for training across the specialties with coordination in the form of symposia in collaboration with pediatrics and social medicine—and the oligophrenology should also be treated. But this belongs to the future I do not give much credit to chair in oligophrenology—I believe that the cross-professional character of the discipline can be retained, and the same I feel concerning oligophrenology as an independent specialty I the short view it might increase the prestige of the discipline but I think that we shall abandon further subspecialization and encourage the versatile aspects where no specialty as such, can stand alone

In the discipline of general medicine as well in the postgraduate training of the general practitioner the problems of m r are essential

And from Odense University in Denmark you have a joint suggestion from the disciplines of pediatrics psychiatry human genetics and oligophrenology that it would be a great advance if a lecturership could be arranged in the discipline of m.r and if this person could be a coordinator of the already existing training and improve this

The Odense pediatrician who is against m r as an independent specialty and a chair is in favour for a cross-professional lecturership or another form of teacher appointment with the responsibility for the training in oligophrenology because this training today is too dispersed haphazard and not coordinated and probably not comprehensive enough He continues

The exploration of the etiology and prevention in mental retardation well medical care of mentally retarded patient represent very comprehensive complication and pensive activities for the community And from medical and public point of view an adequate pregraduate medical training in this field its theoretical and practical spects, must be of great importance

Problems concerned with oligophrenology are mentioned by many different disciplines like human genetics, cyto-genetics, molecular biology biochemistry pharmacology clinical chemistry psychiatry clinical psychology pediatrics, general and internal medicine social medicine neurology and so on. Therefore it will be difficult or impossible to give detailed survey of the total training and education in oligophrenology in medical school unless this concept is furnished with very strict operational definition On the other hand, it is essential that the general extent and level of this training is currently evaluated, and that the contribution from the various disciplines are coordinated and reduced to system clear to every student, long leitmotif At young university like that of Odense where the educational programme for many disciplines are neither finally fixed, nor mutually adjusted but currently exposed to modification, the time is hardly ripe for detailed description of the educational activity in this field

The medical chief superintendent from the local institution for mental retardation states as her view

In my opinion the training in m with all the clinical and social problems must take place at the central institution for m. or by physician from the same centre i e one who know the problems and the patients. It can be carried out at the m.r centre or at the University of Odense or at both places alternately

The centre for m.r has undoubtedly the largest material. Perhaps there is also now and then material at the pediatric department in Odense but it will always be on a lesser scale

As far as I know the social department has realized that it is necessary with clinical demonstrations where the patient i present.

The points IV VIII IX, X XI and XII from the questionnaire can be taken care of by the centre for m.r —probably with some hours at the pediatric university clinic.

The point III can be taken care of by the pediatric department point VI by the pediatric department and probably the centre for m r Point V and VII by the Institute for Genetical Pathology and point II probably by a clinical psychologist.

Bertil Hall from Sweden stresses that the most important thing—according to him—is to stimulate the pediatricians to show a greater interest to m r because in many countries it is the pediatrician whom the family first will meet with their m r child and the problems involved (9)

Another Swedish pediatrician makes the following considerations

The magnitude of knowledge required by the students depends of course on the general purpose and aim in the pediatric training. The aim is to giv the students a basic knowledge and practical training in the care of the healthy and sick child. The training in m.r must be considered in relation to the training in general pediatrics. In my opinion the students must be taught a certain amount of knowledge in m.r concerning etiology and this is most important, the helping programmes of the community A more comprehensive intrusion in the problems of m.r belongs to the post graduat training in pediatrics and child psychiatry

From a dental highschool there is a wish for epidemiological research concerning the need for dental treatment among mentally and physically handicapped children and adults

And from another dentist we have the following concrete wishes and suggestions

1 Visits to institutions for children with various forms of physical and mental handicaps were desirable but at present it is impossible due to the large number of students and the few hours in the curriculum.

2 I find that preventive measures concerning the dental health of the mentioned groups must be arranged—for children who live in their own homes as well as for children who are institutionalized The students are thoroughly instructed in the varying problems presented by different groups of children.

3 I find that systematic postgraduate dental education should be established concerning the handicapped child as well as the adult patient.

To round off these statements concerning alterations and improvements the following two statements by young doctors are quoted

In my pregraduate training I did not follow the lectures on this topic—m.r probably primarily because there was no demand for examination in the field the training in m r was integrated in the disciplines of pediatrics, psychiatry general medicine genetics, and social medicine It was covered by limited time in these disciplines—about -4 hours for each discipline All things considered the result of the training was an orientation concerning oligophrenology and its causes, sufficient as a starting point for the basic doctor who in his future career will not be occupied by the special problems of m.r A postgraduate training would be desirable for all physicians who will meet the problems. This would be more appropriat than an enlargement of the field in the pregraduate medical training.

Concerning other handicaps the training was integrated in disciplines as pediatrics, physiotherapy orthopedics, neurology and social medicine. In this field, I feel that an extension was desirable especially concerning treatment rehabilitation training and social legislation The training I got was given as lectures, clinical demonstration but never as symposia which probably would be an advance in an effort to improve our understanding of these special problems and their coherence.

DISCUSSION

The incentive for the growing interest in mental retardation and other handicapping conditions undoubtedly originates primarily from the work of the parents *organizations* all over the world although it has been augmented by the cytogenetic and biochemical discoveries of recent years The criticism which has been presented about the knowledge and efforts made by the *medical profession and the demand for in*creased teaching for students and doctors also originates to some extent from the same parents associations

Which angle should the present problem be viewed from? The parents expectations of what their doctor can do are frequently great occasionally too optimistic. The question is whether criticism is justified when

the doctor fails or disappoints the patients expectations By and large it is reasonable to expect that some of the problems concerned with m.r and o h c. can be solved by the *general practitioner* Other aspects of the problems must be referred to *specialists* in various fields e g paediatricians and psychiatrists to mention the two most important Finally a number of questions and problems exist which can best be solved by doctors who work with these conditions daily i e *experts* who have m r or o h c as their special field. When the problem of whether doctors learn enough during their undergraduate years and later is viewed thus it cannot be answered unequivocally

Naturally weight must be attached to the assertions of the relatives They experience the problems to an extent which those who not experienced them personally can scarcely imagine It is particularly important to pay attention to what the general practitioner can report It is to him that the parents come first with their problems and he frequently follows the family throughout life

Finally the problems involved in the extent and content of a single field of teaching such as m r and o h c must also be illustrated by the university lecturer who is responsible for the balanced and harmonious distribution of the various subjects in his curriculum He must also consider the variations in the structure of society One of these is the tendency in recent years for mentally retarded and individuals with other handicaps to remain in their homes and to become integrated in the surrounding society in a manner which was completely unknown 20–30 years ago This state of affairs shifts the burden of responsibility from the shoulders of the expert in the institution to the general practitioner to a very great extent

There is a risk that acquaintance with the questioner and his intentions may produce a reply which is influenced by this Similarly it is scarcely avoidable that common sympathy for the mentally retarded or individuals with other handicaps to which the populations of many civilized countries have been exposed via the mass media will also influence statements about what is done and what should be done Finally with this background the individual specialist will probably give the impression of an understanding and sympathetic attitude to the problems involved Answers from the teachers and from other responsible instances will possibly have a tendency to express a more positive attitude than there is actual coverage for Here however this can be checked in the answers from students (from USA) and from recently qualified doctors (from Denmark) These show a definite schism between the opinions of teachers and pupils concerning the goals and means of education concerning m r and o.h.c Even if the teachers seldom or never express any opinion about the results of their teaching, a number of the pupils do so and frequently in a negative manner I shall return to this point later

The first question which arises is whether the allegation made by the parents that doctors offer too little help in the problems concerned with m.r is correct It might be that doctors knowledge of the biological conditions was too limited or that the manner in which doctors administer their knowledge is incorrect or injurious for the client and that doctors for example have no understanding of the psychological mechanisms which act in parents and other relatives in critical situations as for example when the early diagnosis is established when a decision is to be made as to whether the patient should be placed in an institution or should remain at home Or is the problem because the doctor has too limited knowledge of the social and paedagogic problems which are so closely associated with mental retardation and other handicapping conditions?

It appears quite distinctly from the replies that the universities are eager to teach the

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The incentive for the growing interest in mental retardation and other handicapping conditions undoubtedly originates primarily from the work of the parents organizations all over the world although it has been augmented by the cytogenetic and biochemical discoveries of recent years The criticism which has been presented about the knowledge and efforts made by the medical profession and the demand for increased teaching for students and doctors also originates to some extent from the same parents associations

Which angle should the present problem be viewed from? The parents expectations of what their doctor can do are frequently great occasionally too optimistic The question is whether criticism is justified when

gate mental retardation or to have special clinics in this field From this part of the world, in particular it is emphasized that the attitude is patient-orientated rather than disease-orientated and it is proposed that social aspects should receive great recognition

For the above-mentioned reasons *Irving Stone* in Appendix 1 comes to the conclusion Perhaps it is time to consider whether we now are ready to train for a specialty in m r Until retardation stands on its own as a recognized specific area of specialization interest in the field will be nothing more than a poor relative to the total profession of medicine *Frank J Menolascino* professor of psychiatry and paediatrics at the Nebraska Psychiatric Institute is also somewhat dismayed by the present state of affairs and says Accordingly we should seriously consider in my opinion a renaissance of specific interest and medical school organisational structure commitment to programmes for the mentally retarded (70)

As suggested previously a few doctors have obtained specialist knowledge on this subject They are however so few that in my opinion the establishment of a new formal medical specialty is not justified also because this would involve segregation and discrimination at a time when efforts are being made to integrate and normalize the mentally retarded and other handicapped individuals An independent medical specialty would scarcely imply more than brief increase in prestige for the medical sector but would hardly benefit the mentally retarded client and his relatives

I would believe rather that new orientation within medical teaching on the whole is necessary in serious attempts at awaking increased interest in this clientele New orientation such as this must also comprize much more positive and sufficient therapeutic orientation than is the case at present. The psychological social and paedagogic powers which are active in the development of every child must be greatly emphasized These factors are entirely fundamental in the case of a mentally handicapped child or a child who is handicapped in another manner Prerequisites for this understanding are that the medical student at an early stage in his career comes into contact with the authorities in the disciplines concerned and develops the same natural respect for these as he had for subjects such as anatomy and biology

It is more difficult to assess the value of a possible professorate in oligophrenology If this can lead to progress in research and communicate towards communication between the medical disciplines involved and towards coordinated teaching in m r then it is to be recommended The idea is positive if a professorate as it has been suggested could have a further aim than the medical faculty and if the holder of this appointment could work outside the institutions and watch the children in their own environment

CONCLUDING REMARKS AND SUGGESTIONS

A survey of the literature and the present investigation confirm the general impression that the training of medical students in mental retardation and other handicapping conditions is sparse without much coordination between the disciplines and most often haphazard or by chance in several countries

Dental students and dentists seem to have better planned courses in m r and o h c pre and postgraduately But the extent of contact by the dentists with these problems is more limited and has another perspective than the medical profession

The interest of the medical students is limited and generally they are not stimulated to work on the topic in the future

The general practitioner and the practising pediatrician are considered to be the key-persons for the continuum of care that has to be developed for each m r child Consequently the pediatricians and the psychiatrist when the child grows older ... a special obligation in this training pre ...duately in the general curriculum and in the postgraduate training programmes where also general and social medicine must share the responsibility

M R should probably not be separated from other handicaps in the training programmes The teaching in this field should be performed mainly on material and problems drawn from persons who live in the community and not from the institutions As a consequence of this m r should not in my opinion be an independent specialty But some physicians must train to be experts in these problems and probably a chair at universities in this topic might encourage research and coordinate the training-capacities of the various medical disciplines

It must be emphasized from the beginning of the training that there are many therapeutic measures in the field of m r and o h c and the student must be confronted with the psychological social and educational problems which are increasingly important in pediatrics and general medicine especially when m r and o h c are involved We must give a high priority to the students understanding and knowledge of these forces in children s development and of the theories and practice of these disciplines and their authorities a par with what we are doing at present concerning anatomy and biology

ACKNOWLEDGEMENTS

Firstly I want to thank very sincerely my secretary Mrs *Inger Lauer* who performed this work with great devotion—and no extra fee

Secondly I appreciate that *m hospital and community* has always given me good working conditions, including possibility for research

Thirdly I am impressed by the enthusiasm with which Dr *Donald Beasley* from New Zealand Dr *Bertil Hall* from Sweden and Dr *Irving Stone* from California performed their part of the work

Sheila Berggren M D Medical Superintendent corrected the language—for which I am thankful

Many other colleagues through the world have contributed by giving information and through inspiring correspondence and discussions, among them Drs *Bernard L. Cohen* from Israel, *Lydia F de Coriat* from Argentina *Gunnar* and *Rosemary Dybwad* from USA, *Karl Grunewald* from Sweden, *Kenneth S Holt* and *R Michael Hensley* from England, *Robert B Kugel Frank J Menolascino* and *Donald J Stedman* from USA My thanks go to everyone

Finally Mme *Yvonne Posternak* from Switzerland President and Dr *Renée Portray* from Belgium, General Secretary of the International League of Societies for the Mentally Handicapped have followed the project with great interest. It is due to their goodwill and efforts that this publication has been made possible by the economic support of the *League*

REFERENCES

1 Andersen S end Aage Åndsvages tandpleje Danmark *Tandlåkartidningen 63* 728–733 1971 N 20 21 and 22

2 Benton F C Graduate training program in mental retardation for professional personnel. *Proc nd I t Congr M nt Retard* Vienna 1961 Aug. 14–19 Part II pp 205–207 S Karger Basel. 1963

3 Bradley Ch., Medical education in mental deficiency *Amer J Ment Def* 58 310–315 1953

4 Brown, R. H. & Warren, S. A. The handicapped child—a challenge to dentistry *NZ Dent J 61* 3 1965

5 Dybwad, G Pediatrics and Mental Retardation A continuing challenge Remark on Receiving the C. Anderson Aldrich Award Amer Acad Pediat. Chicago Oct. 1st. 1973

6. Editorial Pediatric responsibilities in mental retardation *J Pediat 61* 491–499 196_

7 Gardner George E. Mental retardation as part of the training program in child psychiatry *Proc of the First International Medical Conference on Mental Reta dation* July 27–31 1959 Grune & Stratton New York, 1960 pp. 505–515

8. Gammonn Samuel T The university affiliated facility program for the mentally retarded Miami Florida 4th symposium *Proc I International Congre of th I ternational A for the Scientific Stud of Mental Deficienc* Sept. 1–20 1967 Michael Jackson Publ C London, 1969 pp 814–818.

9 Hall B Pers. communication 1973

10 Haadman Darrell A Co-operativ programmes of training and research in mental etardation in the United States and Canada *Proc of the London Conferenc on he Scientific Stud of M ntal Retardation* July 4–29 1960 May & Baker Dagenham England 196_ Vol I pp 165–170

11 Holt, K S & Huntley R M C Mental Subnormality Medical Training in Britai *J Medical Educ 7* 197 20_ 1973

12 Jago J You can treat handicapped children *Dent Mag 76* 111 1959

13 Jago J D The plac of child dental health in the undergraduate curriculum *A stral Orthodon J 2* 49–5? 1971

14 Jolly Hugh The role of the paediatrician in the care of the mentall handicapped *Dev Med Child Neurol 13* 40–4 1971

15 Knobloch Hilda Teaching about mental subnormality to the medical student and physicia A conference report *Pediatric 31* 146–150 1963

16 Koch Richard Graliker Bett V Sands Russell & Parmelee Arthu H E luation of parental satisfaction with the medical care of retarded child. *Pediatric 23* 58_ 584 1959

17 Kugel R B Pers communication 1973

18 MacFarlane A C Dental Health in ment l deficiency hospitals *Proc of the London Conferenc on th Scientific Study of Ment l Deficiency* J ly 4–29 1960, May & Baker Dagenham England 196_ pp 189–198.

19 Massler M Review of the problems in dealing with the handicapped ch ld *J Dent Educ 21* 63 1957

20 Menolascino F J Pers. communication 1973

21 *Mental etardation acti ities. University-affiliated facilities f r th developmentally disabled* Dept. of Health Education, and W lfare, Washington, March 1972, pp 37

22 *Ment l retardation construction program. Uni er ity-affiliated faciliti* Dept. of Health Education, and Welfare W shington, 1971

23 Olsen N H. The dental care of sick and handicapped children. *Dent Clin N Amer* Nov 1961 p 739

24 *PCMR-message* September 1967 No. 6, pp. 1–7

25 Pearson Paul H The physician role i diagnosis and management of the mentally retarded *Ped Clin North America 15* 835–859 1968

26 Pilkington, Th. L. *Problem and Technique in Teaching Mental Deficiency* I.A.S.S.N D 3rd congress, the Hague September 4–1_ 1973

27 Pitt, David Medical care mental retardation. *Med J Australia* 404–408 1964

28 Powers, Grover F Professional education and mental retardation. *Pediatrics 20* 1088–1094 1957

29 Stedman, Donald J The training of physicians in mental retardation I *Mental Retardation* pp 6–7 1966 October

30 S stu Bjarne Et program for studentundervisning tannbehandling handicappede barn. *Tandlåkartidningen* årgang 63 nr 20, 1 22, pp 740–744 1971

31 Whitney E. A Preventing mental deficiency t students. *Amer J Men Defic 50* 54 1945

32 Wittson Cecil, L., Advantages and problems of university clinical research center for mental retardation *Proc I ternat Copenhagen Congre on the Scientific Study of Mental Retardation*, August 7–14 1964 vol I pp 66–67 Statens Åndsvrage forsorg, Copenhagen, 1964

33 Wittson, Cecil L & Kugel Robert B A medical college program for mental retardation. *Proc of the Firs Congress of he I ternational Ass for the Scientific Study of Mental Deficienc* Sept 12 20 1967 Michael Jackson Publ C London 1968 pp 963 (only mentioned by title).

34 Yannet, Herman A pediatric interne and resident training program integrated with training school for the mentally retarded *Pediatrics 20* 139–147 1957

35 Øster J Adams, M., Sletved H & Stone I Manpower Development in M R *Third Internat Congr of the IASSMD* the Hague Sept 1973

APPENDIX I

USA

From California we have a material which has been collected by Dr *Irving Stone* He got responses from the following institutions

University of California–Irvine Medical School

University of California–Los Angeles Medical School

University of California–Davis Medical School

University of the Pacific–Dental School

Loma Linda University

Unfortunately the number of responses from the students and the University administration was low due to the fact that we probably picked a poor time of the year for it (May) when most of the colleges and universities were completing their academic ears The students were busy—and the uni ersities too

Irving Stone has summarized the results in the following way

When we study the responses of administrators of the three California medical schools which responded to our questionnaire we find that there are varying opinions to the degree of exposure in mental retardation that thei student receive in their training, the number exposed to it, the length of time devoted to mental retardation, and the subjects covered Thus, it appears there is a need for the development of some uniformity in the training.

One of the big differences between the three school only 104 or les than 50% of their total enrollment, received some training mental retardation Another with 764 students, claimed that all were xposed to the subject. The first school stated that approximately 10 hours a year is devoted to mental retardation the other two schools stated that it varied between 4-20 hours a year

It is interesting that lectures or ymposia were little used, a clinical observations and ward teaching rounds were the preferred method All schools admitted that there is no textbook in mental retardation used Either there is no textbook found suitable for medical student or because so little time spent in cla srooms where mental retardation is discussed separat subject that a textbook would have little alue

Oen of the big differences betw en the three school is that the one which claim greatest exposure to mental retardation I the one with the closer affiliation t a *State hospital for the retarded* Some members of the hospital staff have teaching posts in the Medical School and faculty members have part-time staff positions t the hospital or as consultants.

Even the school with the greatest exposure to retardation does not report it includes lectures on the principles and philosophy of mental retardation but rather includes retardation as part of lecture on development and the central nervous system disorders.

Another of the schools provides lectures in subject omitted above and in addition does not consider retardation when presenting early diagnosis and testing procedures. Mental retardation is offered as an elective during the residency program. A result some tudents do accept the opportunity for 3–6 month elective at the Stat hospital

Responses from 40% of the medical student and those in post graduat training in mental retardation consisted of 10 hours or less. Courses in pediatrics, orthopedic clinic and pediatric neurology clinic were most helpful in the understanding of mental retardation Psychiatry was thought helpful too However 84% of the respondent stated they were not stimulated to work with the retarded as result of their training The general lack of interest and of stimulating exposure during training were cited as major reasons for their disinterest. Many thought more lectures in the subject would be helpful others deplored the short time de voted to instruction and thought more time spent l hospital for the retarded would provide greater ppor tunity for understanding the field of work.

Those who have completed training lmost invariably stated they have not worked with the retarded since training Most either considered working with the re tarded not stimulating or rewarding or else were not certain Reasons given for this were that the prognosis is poor progress is too slow it is depressing, or there is poor positive feedback. One even stated that working with the retarded seem more suited to women and mothers. Others stated that there i no specific or satisfactory treatment that medicine ha little to offer or that training in mental retardation should not be mandatory

It is evident at least in California, medical training in mental retardation inadequate in meeting the needs of those completing medical training or in stimulating an interest in working in this field The time devoted to retardation, a lack of clearly defined courses no text material and inadequate clinical contact, beyond observation, are important factors. There should be greater opportunity afforded for follow-up of individual cases

Until retardation stands on it own recognized specific area of pecialization interest in the field will be nothing more than poor relative to the total profession of medicine The U iversity affiliated programs

in the United States is one w y of focusing the attention of the medical professionals to mental retardation even if training i essentially postgraduate

Perhaps it i time to consider whether w are now ready to train for specialty in Mental Retardation. Certainly the need is there for medical practitioners who ha greater knowledge than was formerly available

APPENDIX

NEW ZEALAND AND AUSTRALIA

Dr Donald Beasley from New Zealand has undertaken the responsibility for inquiries in New Zealand and Australia. He used the Danish questionnaire although in a slightly modified form

NEW ZEALAND

Auckland

From the *Medical School* of the University in Auckland there is an answer from which it is quite clear that much teaching is given in mental retardation and other handicapping conditions They seem to attach the greatest importance to general principles philosophy and treatment

Most part of the training is performed as clinical demonstrations

The teaching is equally distributed among professor lecturer and others and the students were very interested

As an answer to Dr Beasley s considerations It is important to avoid the fallacy of the concept of a single handicap or of exclusive categories of handicap —physical emotional intellectual disabilities overlap so often in children and in our approach to pediatric departments and departments of community medicine it would perhaps be wise for us to acknowledge this recognizing that some of them may not have programmes for the teaching of students exclusively in mental retardation but in the whole range of handicapping conditions of childhood What is your practice?" they answer To teach the lot—with emphasis on prevention and on rehabilitation (if possible)

Under any additional comments" they state Too much money and time spent on the individual Services within New Zealand spread and often ineffective despite funding—both for patient care and research

Finally they suggest and recommend further research and better training.

Otago

From the Department of *Pediatrics* and Child Health University in Otago Dunedin New Zealand they found the filling in of this form a very difficult task because our teaching was never in compartments and is now less so than it has ever been However I think the figures I have given are reasonably correct and include the activities of other departments such as Human Genetics and Psychological Medicine though only in the pediatric age group

The training in mental retardation covers 31 lessons and 46 lessons in other handicapping conditions In both fields priority is given to care and nursing, social and psychological implications treatment and parents problems

The teaching is given partly as lectures and symposia, partly as clinical demonstrations and to a less extent as a visit to institutions for mentally retarded and work in outpatient clinics

It is given by professor and lecturers.

Used textbooks are Hutchison. Practical Pediatric Problems Recommended Kershaw Handicapped Children

The students interest is good

As an answer to Beasley s question quoted above they answer 'Our studies are patient-orientated rather than disease orien

APPENDIX I

USA

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When we study the responses of administrators of the three California medical schools which responded to our questionnaire, we find that there are varying opinions as to the degree of exposure to mental retardation that their students receive in their training, the number exposed to it, the length of time devoted *to mental retardation, and the subjects covered. Thus it appears there is a need for the development of some uniformity in the training.*

One of the big differences between the three schools: *only 104, or less than 50% of their total enrollment,* received some training in mental retardation. Another, with 264 students, claimed that all were exposed to the subject. The first school stated that approximately 10 hours a year is devoted to mental retardation; the other two schools stated that it varied between 4–30 hours a year.

It is interesting that lectures or symposia were little used, as clinical observations and ward teaching rounds were the preferred methods. All schools admitted that there is no textbook in mental retardation used. Either there is no textbook found suitable for medical students or because so little time is spent in classroom where mental retardation is discussed as a separate subject that a textbook would have little value.

Oen of the big differences between the three schools is that the one which claims greatest exposure to mental retardation is the one with the closer affiliation to a State hospital for the retarded. Some members of the hospital's staff have teaching posts at the Medical School and faculty members have part-time staff positions at the hospital or as consultants.

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Until retardation stands on its own as a recognized, specific area of specialization, interest in the field will be nothing more than a poor relative to the total profession of medicine. The University affiliated programs

Postgraduate training is incorporated in resident and family doctor meetings

The responsible teacher adds as his personal opinion that "it is quite unwise to separate out mental retardation" and he finishes with a suggestion for more money for research workers including social workers

From the Institute of *Preventive and Social Medicine* it is stated that they spend two hours on mental retardation and four hours on other handicapping conditions with much importance attached to social and psychological implications helping programmes parents problems and general principles.

The teaching is given as lectures and by professor and lecturers

The students interest is the same as in other disciplines

They agree with Beasley s considerations concerning programmes in the whole range of handicapping conditions in childhood

Personally the replier comments The subject area is not overlooked but curriculum difficulties made very hard any useful integrated approach at undergraduate level

Adelaide

From the University of Adelaide South Australia, there is the following good answer

I would agree with Dr Beasley comment (concerning the teaching of student as the whole range of handicapping conditions in childhood) and find (for this reason) it would be impossible to give accurate answers to the question

We are currently endeavouring to arrange rotation for registrars through the State mental retardation hospital This will be dependent upon accreditation of such post training for fellowship of the Royal Australian College Physicians (equivalent to Board Qualified)

Concerning further research and better training Both of these should be directed toward early detection and prevention of mental retardation, as these will improve the quality of care for the mentally retarded

Furthermore he adds as his personal comment

In view of the strong movement to a oid emphazing that mentally retarded children are different from children suffering illnesses and problems (with which I entirely agree) it seems wrong to teach course in mental retardation separate from general pediatrics and community medicine

In pediatric our students are introduced to mentally retarded children in their first week, part of developmental assessment. They continue to see such children throughout their pediatric course as part of their general training

We also run project ystem in which the student hoose their ow topic. Invariably at least one of the fou topics chosen is about mental retardation in some form.

Presently there committee investigating improved relations between the mental retardation hospital and the pediatric hospital There is strong element of feeling that special clinic would be undesirable in removing the mentally retarded from the general mill of pediatrics and hence depriv both under and postgraduate training of valuable material

Queensland

From the University of Queensland Department of *Psychological Medicine* we have the following answer

It should be borne in mind that we are in the process of curriculum change and that in later years more time might be devoted to problems of mental retardation than is given at present

In fifth year our medical student are given course of ystematic lectures on psychiatry and these will include tw lectures on mental subnormality which usually are given by our lecturer in clinical psychology Bearing in mind the short amount of time ailable concentration turns on early diagnosis, such treatment as might be ailable and the social and psychological implications The students are not provided with any pecific textbook other than those covering the whole field of psychiatry the majority of hich ha chapter on mental retardation

In their clinical term which currently last only four eek the main emphasis of teaching is on adult psychiatry Consequently any teaching on mental retardation is purely incidental to the type of case material that might be available during their clinical work However they do have one clinical demonstration during this period at the local mental hospital where number of different types of mental retardation are demonstrated for their benefit Again, the emphasis is particularly upon recognition and diagnosis with some discussion of aetiology both in terms of chromosomal and genetic influence

A far as postgraduat study is concerned there is no special provision made for the study of mental retardation in Queensland to my knowledge. However some psychiatrists in training hav special perienc in the Department of Child Guidance and Welfare or alternatively at the local mental hospital which ha

unit for the management of children and adolescent with this condition

From the Department of *Dentistry* the lecturer in dentistry for children gives a very detailed account

clinical training of dental students takes place in virtual isolation from that of medical students likewise our staff has almost no contact with that of the Medical School and especially with the Department of Child Health.

As to the teaching he writes

At present there are only 60 hours of clinical training in pedodontics Emphasis on basic training for *normal* children A lecture is given, some students would be allocated a m or other handicapped child to treat.

A sessment procedures, early diagnosis, clinical cytogenetics and genetic counselling are not included

The instructions are given by lecturers.

Mainly the students are interested

Arrange visits to subnormal blind deaf and autistic children s centers.

One of our lecturers J D Jago has had extensive experienc (10 years full-time) in working with primarily m.r children, performing dental treatment.

Further research will be developed as more staff and funds become available—present interest ar in epidemiology of dental disease in handicapped children.

Better training cannot be done until a substantial curriculum change is made to provide both additional time in the course for dentistry for children and appointment of additional staff At present the prospect for this negligible

Especially the list of references discloses a very thorough interest in the mentally retarded and otherwise handicapped children

From the Department of *Child Health* Queensland it is mentioned that a large amount of hours are spent on diverse aspects in many different departments

Western Australia

From Western Australia Mental Health Services the answer to the questionnaire seems to have been made by the *Child Health* Department in cooperation with the physician-superintendent from the *Mental Deficiency* Division

The student seem to ha 1 hour training in mental retardation—primarily gen l principles and philosophy

Most of the teaching is given as clinical demonstrations—but also lectures and symposia

The instruction is given by lecturers

The student interest is moderate

The practice here is to consider all facet of children s handicaps, physical mental and social.

Postgraduate training of physicians in mental retardation is not dealt with s a separate item but from time to time is included in general pediatric postgraduate courses of study for general practitioners. The subject will be included in recommended 5 year postgraduate programme for the senior qualification of F R.A.C P in pediatrics. It will mean that prospective career consultant pediatricians will have to do this as a requisite part of thei training programme.

The subject should be taught as part of pediatrics rather than psychiatry—social aspect should receive great recognition.

Further suggestions and recommendations. For greate emphasis on methods of counselling, use of social workers and other social agencies.

An attempt by Dr H and myself some years ago to find out what medical officers working in the field felt that students should be taught elicited a nil response

Furthermore you have the following comments from the chief of the Child Health Department

The structu d programme on mental retardation is recorded in Dr Hamilton reply to the questionnaire Mental retardation is also taught throughout the main paediatric course held at the Princes Margaret Hospital for Children Perth but the subject is included in other broad topic such as inborn errors of metabolism genetics child development Children with mental and psycho-social problems represent a considerable part of inpatients and outpatients and are used for teaching purposes The subject of mental retardation and the care of mentally handicapped children runs consistently through the whole ten eeks block paediatric programme At the main linical conference of the week each medical unit has in attendance child psychiatrist social worker and the chairman of the assessment unit for children with multiple handicaps.

Teaching on mental retardation is given by the physician belonging to each unit. These would range from professor through other members of the university sub-professorial staff to visiting clinicians.

A neurology conference followed by a neurology C P C is held each week and a considerable number of children who are presented have mental retardation accompanying their neurological defect

P M.H lso has ward of 28 beds and cot for the care of profoundly retarded immobile children who are untrainable

Several members of the staff of Irrabeena, the Mental Deficiency Division of the Mental Health Services of Western Australia, also attend P M H for conferences seminars and for the assessment clinic These

include medical officers, psychologist and social workers.

These remarks are supplementary to the structured programme the report of which has been compiled by Dr [illegible] J. L. Ham hoo

Students are interested in such teaching if it is dealt with at the clinical level. They are not so interested in visiting institutions and being shown the kitchens or how the records are kept.

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksell Tryckeri AB, Uppsala, Sweden, without charge.)

181. Koch, Günther, Lung Function and Acid-Base Balance in the Newborn Infant. 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. 1968
185. Andersen, Else, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. 1968
187. Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. 1968
188. Meeuwisse, Gerard W. and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. 1969
189. Fällström, S. P., *On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants.* 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. 1969
191. Koivikko, Antti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kasanen, Antti, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. 1969
196. Rosberg, Georg, *Social and Psychological Factors Influencing Hospital Admission of Children.* 1969
197. Saxén, Eiva, Pseudomonas Infections in a Paediatric Surgical Unit. 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. 1969
199. Vikstedt, Hidde, Tape Recordings of the Electrocardiogram in Newborn Infants. 1969
200. Sanjur, Diva M., Cravioto, Joaquin, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Pre-Industrial Setting. A Sociocultural Approach. 1970
201. Sutherland, Lorne E., Hartroft, Phyllis, Balis, John U., Bailey, John D. and Lynch, Heather J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Kindred, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. 1970
202. Fomon, Samuel J., Filer Jr, L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. 1970
204. Berg, Kristian, *Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age.* Effects of Physical Training and Improved Nutrition. 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Matti Dahl. 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Child-psychiatric and Electroencephalographic Study on Primary School Children in Umeå. 1970
210. Rosberg, Georg, Parental Attitudes in Pediatric Hospital Admissions. 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. 1971
212. Hakulinen, Alpo, Urinary Excretion of Vanillylmandelic Acid of *Children in Normal and Certain Pathological Conditions.* 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. 1971
214. Samuelson, Göte, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. 1971
215. Berggren, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped Children. 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. 1971
217. *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposium.* Stockholm, August 30–September 1, 1970. Edited by Claes Thorén. 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. 1971
219. Jaffé, Doris, Hartroft, Stanley, Manning, Mary and Eleta, Graciela, Coronary Arteries in Newborn Children. Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. 1971
220. Hallman, Niilo, Bäckström, Leena, Kantero, Riitta-Liisa and Tiisala, Riitta, *Studies on Growth of Finnish Children from Birth to Ten Years.* 1971
221. Bohman, Michael, A Comparative Study of Adopted Children, Foster Children and Children in Their Biological Environment Born after Undesired Pregnancies. 1971
222. Jukarainen, Erkki, Plasma Magnesium Levels during the First Five Days of Life. 1971
223. Fomon, Samuel J., Thomas, Lora N., Filer, Jr., L. J., Ziegler, Ekhard E., and Leonard, Michael T., Food Consumption and Growth of Normal Infants Fed Milk-based Formulas. 1971
224. Klackenberg, Gunnar, A Prospective Longitudinal Study of Children. Data on Psychic Health and Development up to 8 Years of Age. 1971
225. Suoninen, Pekka, *Physical Growth of Children with Congenital Heart Disease. Pre- and Postoperative Study of 355 Cases.* 1971
226. Hagberg, Bengt, Sanner, Gunnar, and Steen, Monica, The Dysequilibrium Syndrome in Cerebral Palsy. Clinical Aspects and Treatment. 1972
227. Anttila, Raimo, Renal Involvement in Juvenile Rheumatoid Arthritis. A Clinical and Histopathological Study. 1972
228. *Hämäläinen, Pentti, Wendelin, Heikki, Ekelöw, Gunn, and Paasio, Martin,* Chronic Respiratory Paralysis. A Clinical Study of 13 Patients in Long-term Respirator Treatment after Poliomyelitis. 1972
229. Bucci, Giovanni, Scalamandrè, Antonio, Savignoni, Pier Giorgio, Mendicini, Mariano, Picece-Bucci, Silvana, and with technical collaboration of Pacifico, Lorenzo, *The Systemic Systolic Blood Pressure of Newborns with Low Weight. A Multiple Regression Analysis.* 1972
230. Asmundsson, Ebbe, Late Prognosis of Children Born into Tuberculous Households. The Effect of Isolation and Simultaneous BCG-vaccination. 1972
231. Stensland Junker, Karin, Selective Attention in Infants and Consecutive Communicative Behavior. 1972
232. Hagne, Ingrid, *Development of the EEG in Normal Infants During the First Year of Life. A Longitudinal Study.* 1972
233. Wendelin, Heikki, Microangiography of the Liver. An Experimental Study of Sheep from the Prenatal to the Postpartum Period. 1972
234. Gerrard, J. W., MacKenzie, J. W. A., Goluboff, N., Garson, J. Z., and Maningas, C. S., *Cow's Milk Allergy: Prevalence and Manifestations in an Unselected Series of Newborns.* 1973
235. Köhler, Lennart, Health Control of Four Year-Old Children. An Epidemiological Study of Child Health. 1973
236. *Proceedings of the Seventeenth Nordic Paediatric Congress.* Reykjavik, June 27–June 30, 1973. Edited by Peter Johan Moe. 1973
237. Sillanpää, Matti, Medico-Social Prognosis of Children with Epilepsy. Epidemiological Study and Analysis of 245 Patients. 1973
238. Silwer, Jürgen, von Willebrand's Disease in Sweden. 1973
239. Forsius, Harriet, The Finnish Skolt Lapp Children. A Child Psychiatric Study. 1973
240. *Rearing of Non-identical Twins with Lymphopenic Hypogammaglobulinaemia under Gnotobiotic Conditions.* Edited by W. M. Teller. 1973
241. *Salmi, Toivo T., Haptoglobin Levels in the Plasma of Newborn Infants,* with Special Reference to Infections. 1973
242. Valkeakari, Tuula, Analysis of Serial Echoencephalograms in Healthy Newborn Infants During the First Week of Life. A Comparative Study by One- and Two-dimensional Echoencephalography. 1973
243. Lundström, Nils-Rune, Clinical applications of echocardiography in infants and children. 1974
244. Ahlström, Hans, Studies on Pulmonary Mechanics in Infants. 1974
245. Iversen, Ulla, Hereditary Nephropathy with Hearing Loss "Alport's Syndrome". 1974
246. Oster, Jakob, Training of Medical and Dental Students in Mental Retardation. 1974

Printed in Sweden by Almqvist & Wiksell, Uppsala 1974

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 247 1974

MECHANICS OF BREATHING IN NEWBORN INFANTS WITH PULMONARY DISEASE

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CONTENTS

I INTRODUCTION

Lung disease in newborn infants is a major clinical problem in several respects. It is responsible for a large part of the mortality and morbidity among pre term infants and the care of infants with this kind of disease requires many resources with highly specialized wards and a large staff. Al though research on the pathophysiology diagnostics and therapy in this field is in progress, especially concerning idiopathic respiratory distress syndrome (IRDS) or hyaline membrane disease (HMD) much remains to be done in these respects. Several different diseases present with features which are similar clinically Accordingly differential diagnosis is often difficult There is incomplete uniformity among different centers concerning diagnostic criteria and treatment. In order that the most common, severe disease IRDS may be differentiated from the more benign disorders, clinical diagnoses rely on radiologic assessment and estimation of the magnitude of right-to-left shunt via arterial blood gas measurements. Direct studies of lung function however have not been used in clinical practice and methods suitable for clinical use have not been available. Such methods obviously require special procedures as the patients not can be expected to follow specific requests. As measurement of breathing mechanics requires only a minimum degree of cooperation such methods would be suitable for diagnostics, and for the study of pathophysiology This advantage was observed early and during the last twenty years several groups have published investigations of pulmonary mechanics primarily in healthy new born infants (8, 9 11 14 16 22 36 44) but some also on infants with respiratory distress (10 12 21 37) The most extensive study on IRDS by Chu et al (10) demonstrated low lung compliance to be a constant finding in IRDS. Some earlier studies had reported the same phenomenon in a somewhat more broadly defined group of respiratory distress (12, 1) The low lung compliance in these patients has sometimes been regarded as *pathognomonic for IRDS and has been ascribed* to the reduction in pulmonary surfactant demonstrated in this desease Prod'hom et al (37), however have shown that lung compliance may be decreased in diseases without the right-to-left shunt characteristics of IRDS. Only limited information is available concerning pulmonary resistance in neonatal disease

The purpose of this work was to develop a system suitable for measurement of mechanics of breathing in severely diseased newborn infants; and to apply this system to the study of mechanical parameters as diagnostic criteria in a patient population. Beside the clinical studies theoretical and methodological problems have been stressed as some aspects have been largely ignored in pediatric litterature concerned with the mechanics of breathing. Such problems are particularly relevant because measurements in newborn infants differ in several respects from those in adults and the technique of measurement is extremely critical to valid assessment.

See page 47 for references.

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II THEORETICAL CONSIDERATIONS AND METHODS

Ola Hjalmarson, Torsten Olsson and Martin Riha

Introduction

A great deal of interest has been directed to the mechanical properties of the lungs of newborn infants during the last twenty years. Measurements of ventilatory mechanics, however involve several problems and only a few investigations on pulmonary mechanics in newborns with lung desease have been published. Because of the existing interest in problems of differential diagnosis and monitoring of deseased newborn infants in our departments there was an interest in evaluating mechanical lung parameters in newborns with lung disorders for such purposes.

Many systems have been used to measure flow and volumes in newborn infants during breathing, including pressure or volume-recording body plethysmography (13 14 15 47), inverse plethysmography (17 28), pneumotachography (12) and impedance plethysmography (39). For our purposes we preferred a plethysmographic method for flow and volume measurements, as it would permit examinations to be made during more than a few breaths and under controlled circumstances. Such a method does not require a face mask, with its added dead space and face irritation, and measurements of thoracic gas volume can be made with the same system (6, 29). For this study a flow-displacement body plethysmograph was built and will be described As distinguished from a closed plethysmograph, such a box may have small dimensions without the drawback of high back pressure which may interfere with the ventilatory system, create unfavorable effects due to heat exchange and increase the risk of air leaks. It was also an advantage for us to have flow as the primary output signal as no differentiations were required before embarking on the computer analysis to be described. Essential advantages for measurements and calculations were achieved by combining this plethysmograph with a computer

The purpose of this study

was to construct a system for studies of ventilatory mechanics, based on flow displacement body plethysmography esophageal pressure measurements and a computer system, to be used safely on newborn infants, including the most severely ill patients, to analyze the properties of such a system, to adapt it to a suitable lung model and to analyze the results of measurements on healthy and diseased infants.

Lung mechanics and mechanical lung models

Ventilation implies that mechanical energy developed by the muscles of breathing is used for gas transport to and from the lungs. The muscular force developed applies to the lung at the lung surface (44). During inspiration the inspiratory muscles here cause a pressure driving the lung. Under expiration the lung is driven by its elastic pressure sometimes together with expiratory muscles. During the first phase the expiration during quiet breathing is antagonized by ceasing activity of inspiratory muscles. The pressure difference between lung surface and surrounding atmosphere reflects in every moment on one hand the sum of static and dynamic force applied to the chest wall and opposing forces in the lungs on the other. For a detailed discussion and review of mechanics of breathing the reader is referred to Campbell et al (10)

Simultaneous registration of pleural pressure P_{pl} and flow $\dot{V}$ shows under normal breathing that pressure and flow signals have approximately the

same shape but differ significantly in phase To calculate the mechanical analogue to electrical "admittance" $\dot{V}/P_{pl}$ in an appropriate manner would be an easy way to get an expression of the mechanical function of the ventilatory system in terms of ability to convert pressure developed by the muscles, to ventilatory flow Such an expression is free from any specific assumption on intrinsic mechanical properties of the lung. To get information on the mechanical properties of the lung from flow and pressure redordings assumptions on the lung as a mechanical system, constituting a lung model must be made Theoretical analysis of lung mechanics taking lung elasticity and flow resistance into consideration have resulted in the presentation of lung models defining mechanical parameters relating the pressure applied to the system to different expressions of output (4 44). The significance of the parameters depends on how well the model used describes the course of a breath. These problems have been reviewed by Mead (34). A simple mechanical model describes applied pressure P opposed by elastic resistive and inertial pressures developed by the system according to Newton s third law of motion

$$P(t) = \frac{1}{C} \int_0^t \dot{V}dt + R\dot{V} + I\ddot{V} \qquad (1)$$

$\dot{V}$ and $\ddot{V}$ are the flow and time derivative of flow The equation defines the parameters compliance C resistance R, and inertance I The inertance of the lungs in adults was studied by DuBois (19) and Mead (33) and was found to be low 0.01 $cmH_2O/(l/s^2)$ associated with a pressure amplitude of only 0.02 cmH_2O during quiet breathing (33). There are no measurements of lung inertia in newborn infants available and no data on air velocities in different parts of the airways allowing accurate calculation. From existing morphometric data, however the inertance of the air in the trachea may be estimated and a comparison between newborn infants and adults is shown in Table 1 If the architecture of the bronchial tree and the flow velocities were similar in the newborn and the adult, the calculated four to eight times higher inertance of the trachea in the newborn

Table 1 Tracheal size Inertance I and inertia dependent pressure drop ΔP in the trachea for air acceleration $\ddot{V}$ during quiet breathing in newborn infants and adults.

	Newborn infants	Adults
Area (cm^2)	0.14[1)] 0.77[2)]	3.39
Length (cm)	4.0[1)]	12.0
I ($cmH_2O/l/s^2$)	$3.2 \cdot 10^{-2}$ $1.7 \cdot 10^{-2}$	$3.97 \cdot 10^{-3}$
$\ddot{V}$ (l/s^2)	0.5	2
ΔP (cmH_2O)	0.016, 0.009	0.008

1) Calculated from data from Abt (1).
2) Calculated from data from Engel (21)
Calculations and data for adult according to Mead (33)

would hold for the entire lung compared with the adult. The pressure drop over the trachea due to inertia under quiet breathing, however is similar due to different values of flow acceleration. Wohl et al (49) using the technique with forced oscillations found the resonance frequency to be 3–5 Hz in the total ventilatory system in a material of healthy infants of which 28 where three to four-days old and 29 were one- to fifteen-months. Using the resonance frequency the inertance of the total ventilatory system may be calculated from the formula $I = 1/4\pi^2 f^2 C$ (33). If C is $4 \cdot 10^{-3}$ l/cmH_2O in a newborn infant the inertance is 0.25 – 0.70 $cmH_2O/(l/s^2)$ for the mentioned resonance frequencies. The corresponding calculated value for adults is considerably lower being 0.007 $cmH_2O/(l/s^2)$ (33). Under ordinary breathing, however even these values of inertia implies rather low related pressures in healthy infants of 0.13 – 0.35 cmH_2O corresponding to –5 % of the total pressure swing (see section III) If inertance is unchanged in infants with pulmonary disorders the higher volume accelerations measured (Table 2, page 10) would give higher pressures related to inertia but the proportion of the total pressure variation (see section III) would remain in the same range 2–8 %. The results suggest that inertia is of greater importance in the newborn infant than in adults, but the absolute influence is still small during normal breathing. Neglecting inertia, equation 1 becomes

$$P(t) = \frac{1}{C} \int_0^t \dot{V}dt + R\dot{V} \qquad (2)$$

The equation presented by Rohrer (44) includes another term, KV^2 where K is a constant. Experimental studies in adults have shown that such an expression constitutes a better model when flows are high but equation 2 is well satisfied at ordinary breathing flows (35). In studies of lung mechanics in newborn infants with and without lung disease only equation 2 has been used in combination with simple methods for calculation of R and C from registrations of flow volume and transpulmonary pressure No studies on the validity of the lung model defined by equation 2 in newborn infants have been published as far as we know

Body plethysmography as a method for flow registration and measurement of thoracic gas volumes in newborn infants.

Principles

A body plethysmograph arranged for measurement of flow employs an airtight box enclosing a subject whose airway openings are exposed to the outside. With the subject in place the air inside the box is in connection with the outside only by an opening occupied by a pneumotachograph. During breathing body volume is changing, forcing air to flow in and out through the pneumotachograph recording the flows.

In the following analysis isothermal conditions are supposed and the inertance of the system is neglected. If volume is changed by moving a wall in a system defined by an airfilled room with an outlet presenting a resistance to flow the resistance R generates a pressure change ΔP in the air of the system, or

$$\Delta P = R\dot{V}_R \text{ where} \tag{3}$$

$\dot{V}_R$ is the flow through the resistance This pressure change leads to a compression or decompression of the air corresponding to the compliance C of the system, and

$$\Delta V_{air} = C \ \Delta P \tag{4}$$

if ΔV_{air} is the air volume change in the system due to compression or decompression. Combining equations 3 and 4

$$\Delta V_{air} = RC\dot{V}_R$$

The volume change applied to the system dV_s can then be expressed, either using differentials as

$$dV_s = \dot{V}_R dt + dV_{air}, \tag{5}$$

$$dV_s = \dot{V}_R dt + RC\dot{V}_R \tag{6}$$

or using derivatives as

$$\frac{dV_s}{dt} = \dot{V}_R + RC \frac{d\dot{V}_R}{dt}$$

$$\text{or } \dot{V}_s = \dot{V}_R + RC\ddot{V}_R \tag{7}$$

This means that a volume change applied to the system will give an outflow differing in phase and amplitude from the flow applied, if flow is not constant. The phase and amplitude differences are in proportion to the time constant RC of the system and to the time derivative of flow Equation 7 is useful for understanding the relationship between volume change and recorded flow in the plethysmograph. The equation can be directly applied to the plethysmographic system,

$$\dot{V}_B = \dot{V}_{pn} + (RC)_{box}\ddot{V}_{pn} \tag{8}$$

where $\dot{V}_B$ is body volume change per unit time,
$\dot{V}_{pn}$ is flow through the pneumotachograph and
$\ddot{V}_{pn}$ its time derivative

$(RC)_{box}$ is the product of resistance and compliance of the plethysmograph, constituting its time constant.

Now the change $\dot{V}_B$ of body volume during breathing is the result of changes $\dot{V}_{TG}$ in thoracic gas volume and $\dot{V}_{AG}$ in abdominal gas volume

$$\dot{V}_B = \dot{V}_{TG} \overset{(+)}{-} \dot{V}_{AG} \tag{9}$$

$\dot{V}_{AG}$ is due to compression of abdominal gas during breathing. If abdominal muscles are active during expiration $\dot{V}_{AG}$ has the same sign as $\dot{V}_{TG}$ in all other situations signs differ For small ΔV and isothermal conditions, Boyle Mariotte's law gives

$$\Delta V_{AG} = \Delta P_{adb} \frac{V_{AG}}{P_{BD}} \qquad (10)$$

ΔV_{AG} is the abdominal gas volume change due to compression and decompression.
ΔP_{abd} is the abdominal pressure
P_{BD} barometric pressure minus water vapor pressure
ΔP_{abd} is generated by the flow resistance R_{abd} and the compliance C_{abd} of the abdominal contents and walls, so that

$$\Delta P_{abd} = R_{abd} \dot{V}_{abd} + \frac{\Delta V_{abd}}{C_{abd}} \qquad (11)$$

$\dot{V}_{abd}$ is the volume change per unit time of the abdominal wall. Combining equations 10 and 11 gives after differentiation and arranging

$$\dot{V}_{AG} = \frac{V_{AG}}{P_{BD}} \left(\frac{1}{C} \dot{V}_{abd} + R_{abd} \ddot{V}_{abd}\right). \qquad (12)$$

Under the assumption that alveolar gas pressure P_{alv} is representative for all lung gas during breathing, equation 7 may be directly applied to lung gas and

$$\dot{V}_{TG} = \dot{V}_{aw} + R_{aw} C_{aw} \ddot{V}_{aw}$$

$\dot{V}_{aw}$, $\ddot{V}_{aw}$ is airway flow and flow derivative
R_{aw} is airway resistance. The compliance of lung gas can be expressed by Boyle-Mariotte's law, i.e. for small Δ

$$C = \frac{\Delta V}{\Delta P} = \frac{V_{TG}}{P_{BD}}$$

where V_{TG} is thoracic gas volume. Now

$$\dot{V}_{TG} = \dot{V}_{aw} + R_{aw} \frac{V_{TG}}{P_{BD}} \ddot{V}_{aw} \qquad (13)$$

or defining K_{aw}

$$\dot{V}_{TG} = \dot{V}_{aw} + K_{aw} \ddot{V}_{aw}. \qquad (14)$$

Put in words, there is a difference in phase and amplitude between the air flow through the airways and the corresponding changes in volume of the thoracic gas, depending on airway resistance, thoracic gas volume, barometric pressure and volume acceleration.

Now combining equations 8 and 9

$$\dot{V}_{TG} = \dot{V}_{pn} + (RC)_{box} \ddot{V}_{pn} \left(\mp\right) \frac{V_{AG}}{P_{BD}} \left(\frac{1}{C} \dot{V}_{abd} + R_{abd} \ddot{V}_{abd}\right). \qquad (15)$$

This means that $\dot{V}_{TG}$ is measured by the pneumotachograph with an error depending on the time constant of the box, the time derivative of flow through the pneumotachograph, the part of the body volume change displaced by the abdominal wall, its time derivative and the compliance and resistance of the abdomen, together with abdominal gas volume and barometric pressure.

Similarly, combining equations 14 and 15

$$\dot{V}_{aw} = \dot{V}_{pn} + (RC)_{box} \ddot{V}_{pn} \pm \frac{V_{AG}}{P_{BD}} \left(\frac{1}{C} \dot{V}_{abd} + R_{abd} \ddot{V}_{abd}\right) - K_{aw} \ddot{V}_{aw} \qquad (16)$$

The error in measuring $\dot{V}_{aw}$ by $\dot{V}_{pn}$ is determined by three terms including time derivatives of different flows. When $\ddot{V}_{pn}$ and $\ddot{V}_{aw}$ have the same sign, $\dot{V}_{pn}$ measures $\dot{V}_{aw}$ more accurately than $\dot{V}_{TG}$.

The size of the errors can be estimated from estimations of V_{abd}, K_{aw} and maximum $\ddot{V}_{pn}$ made on healthy infants and infants with pulmonary disorders presented in table 2. In the plethysmograph to be described the time constant was $3.0 \cdot 10^{-2}$. The maximal sizes of the errors can be estimated under the assumption that maximal derivatives of all flows in equation 16 equal $\ddot{V}_{pn}$ at $\dot{V}_{pn} = 0$. The results are presented in table 2. It follows that the influence of abdominal gas under the given conditions is negligible (max V_{AG} <0.1 ml/s) and the influence of the compression of thoracic gas in healthy infants and in infants with lung disorders is small (about 1 ml/s). In infants with airway obstruction, however, especially in combination with an increased thoracic gas volume, lung air compression will be of considerable magnitude. The air compression in the plethysmograph may cause a marked maximal error in the measurement of body volume change (about

Table 2. Calculation of maximal deviations of measured flow from airway flow and thoracic gas volume change

Infant group	Data					Max. deviations			
	V_{TG}	R_l	R_{aw}	R_{lt}	K_{aw}	$\dot{V}_{max}$	$K_{aw}\dot{V}_{aw}$	maxV_{AG}	$K_{box}\dot{V}_{pn}$
	l	$cmH_2O/(l/s)$			s	l/s^2	l/s	l/s	l/s
Healthy	0.087	42	29	13	$2.5\ 10^{-3}$	0.5	$1.3\ 10^{-3}$	$3.3\ 10^{-4}$	$1.5\ 10^{-2}$
IRDS	0.040	69	56	13	$2.2 \cdot 10^{-3}$	1.2	$2.6\ 10^{-3}$	$3.3\ 10^{-4}$	$3.6\ 10^{-2}$
Aspir.syndr	0 072	48	35	13	$2.5\ 10^{-3}$	1 0	$2.5\ 10^{-3}$	$3\ 3\ 10^{-4}$	$3\ 0 \cdot 10^{-2}$
Unclassified lung disorders	0 099	56	43	13	$4\ 3\ 10^{-3}$	1 0	$4.3\ 10^{-3}$	$3.3\ 10^{-4}$	$3.0 \cdot 10^{-2}$
Airway obstr	0.100	150	137	13	$14\ 10^{-3}$	1.5	$21\ 10^{-3}$	$3.3\ 10^{-4}$	$4.5\ 10^{-2}$

The group f diseased infants and values for V_{TG} and R_l are taken from section III except for "airway obstruction which ses values from an infant with Pierre Robin s syndrome Airway resistance R_{aw} in healthy infants sed in the table was measured by Polgar (42) and lung tissue resistance R_{lt} was estimated by subtraction of this value from lung resistance R_l R_{lt} is considered unchanged in disease. $\dot{V}_{max}$ was calculated graphically from recordings of flow in 14 healthy and diseased infants The given values are means f maximal values found when V O

Ma V_{AG} is calculated according t equation III after differentiation. V_{AG} 0 050 l is a rough estimate dP_{abd}/dt sed in equation 10, was calculated graphically from measurements of gastric pressure in 10 healthy and diseased infants. k_{bo} was 0.030

15 ml/s). The values of flow given may be put in relation to the range of maximal flows in healthy newborns 22–85 ml/s.

In conclusion. Abdominal gas has a negligible influence on measurements of ventilatory flow with the result, according to equation 15 that

$$V_{TG} = V_{pn} + (RC)_{box}\dot{V}_{pn} \qquad (17)$$

The flow body plethysmograph may consequently be used for measurement of V_{TG} if V_{pn} is corrected with a term $(RC)_{box}\dot{V}_{pn}$ In infants with normal thoracic gas volumes and airway resistances,

$$V_{aw} \approx V_{TG}$$

At high thoracic gas volumes and airway resistances, the compressibility of the thoracic gas will cause a marked deviation and

$$V_{aw} = V_{TG} - k_{aw}V_{aw}$$

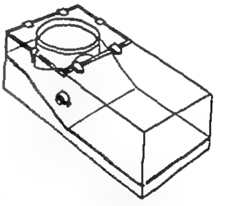

Fig. 1 The body plethysmograph

The body plethysmograph

was made of lucite of thickness 6 mm. The outer dimensions are 19 0 x 25.9 x 61.2 cm. The inner volume is 25 4 l These dimensions permitted the box to be placed inside an incubator (Isolette Airshields Ltd) during measurement assuring the infant an accurate temperature and an adequate humidity at all concentrations of inspired oxygen

Temperature and humidity differences between the inside and outside of the box can be kept small by this arrangement as is essential for measurements of flow. The low air volume in the box is an advantage in reducing the time constant of the system. One part of the upper surface of the plethysmograph can be removed to introduce the infant into the box. The infant is placed on a slanting polyether matress. The removable lid has a circular opening of diameter 12 cm, under which the infant's face is placed. The lid can be locked airtight. The box is tightened around the face of the infant by using a tight fitting latex helmet on the head of the infant. The helmet is kept together with a latex band around the cheek. At the free margin round the face a wide edging of latex is fixed and the free margin of this turned over a low edge of lucite around the circular opening on the lid. After this fixation has been made by a rubber band there is no free air passage round the face of the infant. To immobilize the head and to stabilize the packing a circular cuff of latex filled with polysturene particles, 1–2 mm in diameter is modelled carefully around the face of the infant on the upper surface of the latex edging, resting on a support under the latex edging round the face of the infant. The particle-filled cuff reaches over the edge of the lid. When the cuff is in place the air in it is evacuated by suction, rendering the plethysmograph an airtight and stable packing around the face. The foot-end of the box is elevated about 5 cm during measurements to compensate for the slant of the matress, resulting in a slant of the infant of approximately 20 degrees with the head higher than the feet. Infusion catheters and cables for monitoring purposes can pass the box wall through a small slit tightened by plasticine.

For the measurement of flow through an opening in the box wall a pneumotachograph (type Fleisch nr 1) is fitted in without extra tubing. The pneumotachograph is not heated. It is connected to a pressure transducer (EMT 32, Elema Schönander) and the transducer is connected to a polygraph (Mingograph 81. Elema Schönander), to a tape-recorder (Ampex), an integrator for volume calculation and the computer (page 21). Flow and volume are continously recorded on the tape-recorder and the polygraph. Computations can be made on line or off line by the computer.

Calibration of flow and volume.

Flow was calibrated before or after every study. Air of room temperature was led through a 20 cm long tube of the same inner diameter as the pneumotachograph, then through the unheated pneumotachograph and further through a rotameter (Rota, Aachen). The rotameter was calibrated with a spirometer (Bernstein) for three different flows within the flow range of newborn infants, 30, 43 and 61 ml/s, and one of these standard flows were used for calibration.

Volume was calibrated with the equipment described by recording integrated flow on the polygraph during constant calibration flow over a known period of time. Another method used was to connect a syringe with 2 to 20 ml volume to the pneumotachograph (box lid open) via a tube. A known volume was then given through the pneumotachograph and recorded on the polygraph.

Calibrations were always performed with the pneumotachograph at room temperature with air at a mean temperature of 25°C. Measurements were performed in 33°C as an average. To convert to BTPS all flows and volumes measured were multiplied by the factor 1.03.

The linearity of the flow and volume recording system was investigated. A sensitive rotameter (Rota, Aachen) was calibrated with three constant gas flows at room temperature against a continuously writing spirometer (Bernstein). The rotameter was then connected to an air flow source via the pneumotachograph equipped with a 30 cm long tube with the same inner diameter as the pneumotachograph tube in the inflow end. The deflection of the recorder at zero flow and the calibrated flows (30, 43 and 61 ml/s) were measured (Fig. 2A).

Volumes from syringes, 2–20 ml, were given through the pneumotachograph. The flow signals were integrated and the deflections on the polygraph paper were measured (Fig 2 B).

The resistance of the plethysmograph was measured with a flow of known size led through the empty box from an opening in the lid passing out through the pneumotachograph. The pressure inside the plethysmograph was measured by an open catheter (2 mm diameter) connected to a pressure

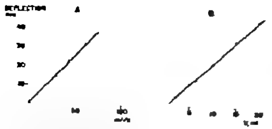

Fig. 2 Linear response of the flow – (A) and volume (B) recording systems

transducer (EMT 32 Elema Schonander). The pressure recording system was calibrated with a water manometer For the given flows (30 43 and 61 ml/s) the resistance was constant 1 1 $cmH_2O/(l/s)$

$\Delta V/\Delta P$-ratio of the plethysmograph was measured during static conditions by introducing 10 and 20 ml of air from a syringe into the box after having tightened the opening in the lid. Pressure inside the box was measured as described above Compliance was measured with only the matress in the box and with a tare volume of 3 litres. The results are means of five determinations and appear in Table 3 The $\Delta V/\Delta P$ ratio was also

Table 3 Determinations of $\Delta V/\Delta P$ of the plethysmograph

Condition	$\Delta V/\Delta P$ ml/cmH_2O
Static. Box empty	26
Static T re 3 0 l	24
Dynamic. Bo ith Infant 1350 4100 g	28 (20 39)

measured during dynamic conditions during volume calibration of the closed plethysmograph as described on page 13 ΔV was measured from the integrated flow and ΔP from box pressure calibrated with a water manometer in 35 infants with body weights 1350–4100 g. The result appears in Table 3

The $\Delta V/\Delta P$ ratio depends on air compressibility compliance of the box walls and mode of heat exchange in the system. In the first experiment isothermal conditions are present, in the second adiabatic circumstances are supposed (9). The difference in $\Delta V/\Delta P$ ratio is, however not significant ($P>0.05$)

The inertia of the plethysmograph was measured as the inertia of the air in the pneumotachograph tube According to Mead (33) $I = k\rho b/0.98A$, where I is intertance in $cmH_2O/(l/s^2)$ k a constant depending on the wave front equal to 2 for laminar flow ρ the density of air i.e. $1.11 \cdot 10^{-3}$ g/cm^3 at body temperature (33) b is the length of the pneumotachograph (6.0 cm) and A its area (2.54 cm^2). Using these values, I is $5.1 \cdot 10^{-3}$ $cmH_2O/(l/s^2)$ The pressure to overcome the inertia of air in the plethysmograph may be calculated to be $2.6 - 3.1 \cdot 10^{-3}$ cmH_2O using values of $\dot{V}$ in table 2. This is about 5% of the total pressure swing in the plethysmograph for average maximum flows in healthy (0.054 l/s) and diseased infants (0.059 l/s) (see section III)

The time constant of the plethysmograph is the product of its flow resistance and $\Delta V/\Delta P$ For the calculations described below the value 30 ms was calculated representing a mean for the box including infants of different sizes.

The dynamic properties of the plethysmograph. As demonstrated above the size of the time constant of the plethysmograph will introduce a considerable error in flow Equation 17 however shows a way to compensate for this error using the derivative of recorded flow and the time constant of the system This was done by the computer by adding to every flow value sampled a quantity equal to the time constant of the system times the derivative of flow The effect of this compensation was tested as follows

Two pneumotachographs (Fleisch nr 1) were connected in series and to a box in which one wall was replaced by a 7" loudspeaker cone which was driven at different frequencies by an oscillator The flow signals from the pressure transducers (EMT 32 Elema Schonander) were displayed on an X Y-oscilloscope and the response of the system at different frequencies was determined (Fig. 3). One pneumotachograph was then put in place in the wall of the plethysmograph, the other still connected to the loudspeaker box, was mounted via a short and wide tube to another opening in the plethysmograph that was otherwise tight The

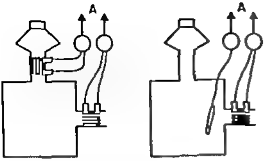

Fig. 3. Tests of frequency dependence of the flow and pressure recording systems.
Left: Test of dynamic properties of the plethysmograph (see text)
Right: Test of dynamic properties of the pressure-recording (esophageal balloon) system and the pneumotachograph (see text).
Circles assign pressure transducers. A is output to computer or oscilloscope.

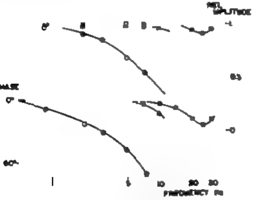

Fig. 4. Amplitude and phase characteristics of the plethysmograph with and without compensation.
□ – □ Two pneumotachographs in series
○ – ○ Uncompensated system
Δ Δ Compensated system (see text)

loudspeaker was again driven at increasing frequencies. The signals from the transducers were analysed with respect to amplitude and phase shift by the computer with and without compensation with the time constant of the plethysmograph (Fig. 4). After flow compensation the plethysmograph box had satisfactory dynamic properties for its purpose

Measurement of thoracic gas volume

The plethysmographic method of DuBois et al (20) was used. The principle of this method is that when the airway opening is occluded during breathing but breathing efforts are maintained, the plethysmographically measured changes ΔV in thoracic gas volume and the corresponding pressure changes ΔP in the airways measured at airway opening proximal to the occlusion can be inserted into Boyle-Mariotte's equation, which is solved for thoracic gas volume V_{TG}

$$V_{TG} \approx \frac{\Delta V}{\Delta P} \; P_{BD} - V_{eq} \qquad (18)$$

presupposing isothermal conditions in the lungs (38) and in this form, $P_{BD} \gg \Delta P$ The volume of the mask used is V_{eq}

Procedure. Infants are studied lying supine in the plethysmograph. A rigid mask (Soucek Mask, Randell-Baker) is gently placed over nose and mouth. The other opening of the mask is tightened by a cork with a hole (diameter 7 mm) for the infant to breath through. A rigid tube (inner diameter 1.5 mm) connects a canula passed through the cork into the mask with a pressure transducer (EMT 34 Elema Schönander) for measurements of mask pressure At the end of an expiration the hole in the cork was suddenly occluded by a finger-tip and ΔV and ΔP were recorded on the polygraph.

Volumes were measured with the plethysmograph arranged as a flow-displacement box as described above or as in the original method (20), as a pressure plethysmograph with the pneumotachograph removed and replaced by a rigid tube connecting box air to a pressure transducer (EMT 32 Elema Schonander). In the former case the volume was calibrated as described on page 11 assuming isothermal conditions in the box. In the latter case a calibration procedure was performed in order to compensate for non-isothermal conditions.

The pneumotachograph (Fleisch 1) was connected to a face mask of the type just described and to a pressure transducer (EMT 34 Elema Schönander). The flow signal could be integrated and recorded on the polygraph (Mingograph 81 Elema Schönander) as volume changes. The mask with pneumotachograph was gently placed airtightly over the nose and mouth of the baby and air volume changes during breathing

were recorded together with box pressure. The pneumotachograph was calibrated for volumes as described on page 11 and box pressure signals could then be calibrated when related to volume signals. The closed plethysmograph method was used in 35 cases and the open box in 95 in the study presented in section III. The mask pressure was calibrated with a water manometer. To exclude leaks and airway obstruction, records were accepted during these measurements only from those breathing efforts in which the recordings of ΔV and ΔP were in phase and with the same shape at visual observation. The mask volume including the volume of the pressure recording system connected, was determined by filling it with water from a calibrated syringe after estimation of the space occupied by parts of the face in the mask. Mask volume was 12 ml. Calculations were made by hand and based on 3 to 15 recorded cycles. Only studies with all observations of V_{TG} within mean ±20 % were accepted.

The validation of the method in newborn infants requires measurements at the same lung volume before and after the introduction of a volume of known size in series with the patient (29).

This validation was done in three infants by connecting an empty glass bottle of volume 112 ml including connections to the infant during some occlusions. Three periods of occlusion were performed with and without the bottle in each infant. Because adiabatic or isothermal conditions do not apply pressure response to volume changes in the system was frequency dependent giving a calculated bottle volume lower than the real one. The tare system was calibrated with volumes (1.0 ml) given at breathing frequency with a syringe giving bottle pressures in the range present during measurements in infants (10 cmH_2O). The virtual bottle volume thus calculated was in good agreement with the values found in the measurements with infants (Table 4).

Comments. In most infants the method was applied without great difficulties. After some trials the mask was tolerated and quiet breathing efforts performed. After some training, occlusion was performed near end expiration even at high breathing frequencies by observing the motion of the abdomen. The phase of a breath in which occlusion was made was revealed by the flow and volume registrations. Recordings made far from end expiratory volume were discarded and no attempts were made to correct measured values exactly to end expiratory level.

Table 4. Validation of measurements of thoracic gas volume.

Bottle volume	112 ml
Virtual bottle volume at mean frequency 37/min	86 ml
Bottle volume calculated from measurements in 3 infants of V_{TG} + bottle volume: 80, 86 and 93 ml; mean volume	86 ml

No systematic differencies in results between the methods used for measuring of ΔV was found. With the calibration method used for the closed system, gas volume changes in the alveoli are a source of error. In infants with ordinary thoracic gas volumes and airway resistances the error dependent on K_{aw} (Table 2), may be expected to be low and this was reflected by the fact that phase shifts were not observed between the signals.

The $\Delta V/\Delta P$ ratio of the tare volume was remarkably frequency dependent. As the ratio was easily measured the correction method used was preferred to introducing heat conducting material in the tare volume used by others. The isothermal conditions in lungs during breathing (38) were supposed to be maintained.

The flow displacement method was preferred in the light of this source of error and the easier calibration procedure.

Measurement of pleural pressure

Measurement of pleural pressure is essential for calculation of lung mechanics. As distinguished from alveolar pressure there is no method adapted to clinical use for measuring pressure on the pleural surface. Recently Agostoni and Miserocchi (3) introduced a technique for measurement of local pleural pressure in animals without opening the pleural space. With their method conditions have been created for evaluation of measurements of pleural pressure performed with indirect tech-

niques. The standard method for estimating pleural pressure is to measure intraesophageal pressure. The validity of this method has been frequently studied. The problems involved can be described with the following questions.

1) To what extent does the recording system reproduce the intraesophageal pressure under static and dynamic conditions?

2) To what extent does the intraesophageal pressure reflect local lung surface pressure?

3) To what extent is the local lung surface pressure in the area near the balloon representative for the entire lung surface?

Ad 1. For measurements on newborn infants, open, water filled esophageal catheters (13, 23, 28) and air filled balloon systems (11, 45, 48) in connection with pressure transducers have been used. In fact, water filled catheters do not measure surface pressure relevant for mechanical studies, but liquid pressure in the esophagus. The difference, however, due to deformation of the esophageal wall is probably insignificant at measurements of tidal changes in esophageal pressure (42). With an air-filled balloon system the volume is critical. A first requirement is that the volume be low enough to exclude the influence of the compliance of the balloon walls on measurements. The total air volume and the physical properties of the catheter must moreover be chosen to provide the system with favourable dynamic properties.

Ad 2. The relation between intraesophageal pressure and lung surface pressure is influenced by several factors. The elasticity of the wall of the esophagus will have an influence, as a fraction of the pleural pressure is taken up by the esophagus, i.e.

$$\Delta P_{pl} - \Delta P_{es} = \Delta P_w, \tag{19}$$

where P_{pl} is pleural pressure

P_{es} is intra-esophageal surface pressure

ΔP_w is the pressure fraction taken up by the esophageal wall.

The change in esophageal pressure will cause an air compression ΔV in the balloon system related to its elastance E_a, or

$$\Delta P_{es} = E_a \, \Delta V \tag{20}$$

Neglecting wall resistance, ΔP_w depends on the elastance E_w of the esophageal wall,

$$\Delta P_w = E_w \Delta V \tag{21}$$

Consequently, combining equation 20 and 21

$$\Delta P_w = \frac{E_w}{E_a} \; \Delta P_{es}$$

or according to equation 19

$$\Delta P_{pl} = \Delta P_{es} \, (1 + \frac{E_w}{E_a}). \tag{22}$$

This means that a change in pleural pressure may be measured as an esophageal pressure change with an error depending on the elastances of the esophagus and the recording system. The corresponding expression, presented by Milic Emili and Petit (36), seems to be somewhat incorrect. The difference, however, has a negligible influence on estimations made of the influence of esophageal elastance on measurements of pleural pressure in the newborn, cited below (27, 45). The elastance of the esophagus is influenced by the degree of its tension and this is related to lung volume (27) and body position (22). The elastance of the recording system depends on the volume-pressure coefficient of the catheter and transducer and, in air-filled systems, on the compressibility of the air and to air volume in the system. The elastance of the esophagus has been measured in newborn infants by Senterre and Geubelle to be 14.4±3.4 cmH_2O/ml, and the error calculated for an elastance of the recording system of 250 cmH_2O/ml was about 6 % (45).

Another source of error are artefacts due to peristaltic pressure waves, but these are normally obvious during the recording. The presence of liquid or air in the esophagus affects volume and compressibility and is a source of error. Special problems will occur if there is a communication between the esophagus and the outer air or stomach gas during any phase of a breath (8).

Extraesophageal structures are expected to influence the relation between esophageal pressure and lung surface pressure. So may the weight of the mediastinal tissues influence this relation and

this effect is expected to be related to body position. Local effects of the trachea and of heart beats also influence the measurements (22, 30 32, 41).

Consequently a difference in absolute pressure between the esophagus and lung surface is to be expected at least in the supine position. The position of the catheter and/or balloon is here of some importance. Registrations made from the lower third of the esophagus avoid the influence of the trachea and of motions of neck and head (37).

Pressure variations in pneumothorax cavities and in the esophagus have been shown to be in good agreement in infants (7 16). However techniques used for direct measurements of pleural pressure are critical due to interference with lung shape (31) With the noninvasive technique of Agostoni and Miserocchi (3), where parietal pleura is dissected free and put under measurable pressures and its motion is studied during breathing, good agreement was noted in supine dogs between tidal changes in esophageal pressure and local pleural pressure in frontal and dorsal parts of the chest.

In conclusion, measurements of *absolute* pleural pressure by means of esophagus pressure may imply considerable errors at least in supine position. If the volume of the balloon is kept low the recording system has satisfactory dynamic properties and the balloon is placed in the lower part of the esophagus, recorded pressure variations are in good agreement with the variations in pleural pressure at least as far as healthy adults infants and animals are concerned

Ad 3 As previously mentioned, it has been shown in supine dogs that pressure variations in the esophagus do not significantly differ from pleural pressure variations, in both the upper and the lower part of thorax, although individual variations do exist (3). Thus the pressure variation in the esophagus during breathing seems to reflect the pressure variation over wide lung surface areas in healthy individuals. Direct measurements of differences in pleural pressure variations on different parts of lung surface in newborn infants with lung diseases have not been performed, and consequently it is unknown whether lung diseases change the relations between pleural pressure and esophageal pressure

The esophageal-pressure recording system used in the present study is an air-filled balloon catheter connected to a pressure transducer with a stiff membrane (EMT 34 Elema Schönander) The latex balloon (manufactured by Nordiska Latex fabriken, Torekov) is 5 cm long, perimeter 20 mm. It is glued to a 60 cm polyethylene chateter (Intramedic) with inner diameter of 1 1 mm. Five to ten holes with diameters 0.5—1.0 mm are cut in the end enclosed in the balloon. The other end is connected to a stopcock which is connected to the pressure transducer The signals are recorded on the polygraph. The volume-pressure coefficient of the transducer is 2.2 10^{-7} ml/ cmH_2O Before measurement the balloon is emptied until its walls just adhere to each other and the stopcock is closed. It is introduced through one nostril and pushed down into the esophagus and 0.25 ml air is injected into the system by a syringe (max. volume 1 0 ml). After connecting the catheter to the pressure transducer the balloon is gently pushed further to the stomach which position is indicated by positive pressure deflexions during breathing, and then withdrawn 5 cm and fixed.

Calibration. The pressure transducer was calibrated with a water manometer immediately before or after every study

The volume-pressure relation of the pressure recording system is demonstrated in figure 5 Zero volume refers to the volume of the system after evacuating air from the balloon described above. The elasticity of the balloon walls does not influence the pressure measurements in the volume range 0.25–0 6 ml.

The dynamic properties of the system were studied by examining its response to a square wave The balloon system was filled with 0.25 ml of air and the balloon with one part of the catheter was placed in a rubber balloon which then was filled with about 5 litres of air under tension of the balloon walls. After tightening, the rubber balloon

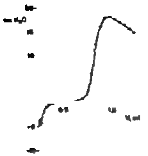

Fig. 5. Volume-pressure relation of the pressure recording system (see text).

was suspended so that the enclosed latex balloon hung freely. The balloon was burst by a very gently applied needle-prick, and the pressure response registered on the recorder during high paper speed. The overswing was less than 5 % of the total response deflection, and the response time between 10 and 90 % of total deflection was 0.01 s ± 0.005 s, corresponding to a bandwidth for this type of system of about 40 Hz. The dynamic properties of the pressure recording system were also examined together with the pneumotachograph (Fig. 3). A loudspeaker was mounted in one wall of a small chamber with the pneumotachograph in an outlet in another wall. A balloon catheter was enclosed in the chamber and the loudspeaker produced sinus waves signals at different frequencies. The flow and pressure signals from the pressure transducers were recorded on an oscilloscope and phase and amplitude differences in signals were measured (Table 5).

Neglecting inertia, the dynamic properties of the pressure recording system may be supposed to be determined by its resistance R_p and its compliance C_p, and the difference in pressure between the esophageal end of the catheter and the chamber of the pressure transducer ΔP_p then is

$$\Delta P_p = R_pC_p \frac{dp}{dt} \quad \text{or}$$

$$P_{es} = P_p + R_pC_p \frac{dp}{dt}$$

where P_p is the pressure in the pressure transducer and P_{es} is the pressure at the esophageal end of the catheter. R_p was determined as the resistance of the catheter and was $6.8 \cdot 10^3$ $cmH_2O/(l/s)$. C_p was not significantly influenced by the $\Delta V/\Delta p$-coefficient of the pressure transducer as this was much lower than that of air. C_p, hence due to air compressibility was $0.7 \cdot 10^{-6}$ l/cmH_2O and R_pC_p $4.8 \cdot 10^{-3}$ s. This time constant can be translated to a phase difference φ assuming sinus signals, and

$$\operatorname{tg} \varphi = 2 \pi f RC$$

where f is the frequency in Hz. Assuming the same approximation, the pressure recording system and the pneumotachograph put together in series as described above have a mean time constant of $3.8 \cdot 10^{-3}$ s, determined from observed phase differences (Table 5). The error in the pressure measurements with respect to flow is hence in every moment $3.8 \frac{dp}{dt} \cdot 10^{-3}$ cmH_2O

Table 5. Differences in phase and amplitude between pressure and flow recordings at different sinus frequencies.

Frequency (Hz)	Phase difference	Amplitude difference
2	<5	< 10 %
5	5.8	< 10 %
7	11	< 10 %
10	13	< 10 %

Corrections of the pressure signal. The pressure signal could be corrected for the error due to the time constant of the system in analogy with the flow signal, described on page 12, using equation 23. Facilities for such a compensation was included in the computer program.

Comment. The dynamic properties of the methods for pressure and flow measurements are critical in studies of pulmonary mechanics. The phase difference between pressure and flow signals involves most of the information on pulmonary compliance and even small phase errors must be avoided.

The first procedure to be performed to reduce this type of error must be to reduce the time constants in the recording systems. This was att

what concerns the flow recording system be reducing the volume of the plethysmograph. If a screen mesh pneumotachograph had been used the resistance could have been considerably lower. The good linear response of the pneumotachograph used even at very low flows, together with the favourable signal-to-noise-ratio reached however was in favour of the tube pneumotachograph used. The advantages mentioned were of significance as the important error in flow due to the time constant of the plethysmograph could be corrected. The time constant of the pressure recording system can be reduced by increasing the inner diameter of the catheter. This should have involved an increase of the outer diameter which was avoided considering small, pre-term infants were to be studied. Correction of remaining, significant errors in recorded signals may be performed in different ways and methods for flow correction have been published (46, 47). For the recording system presented the flow correction is performed automatically and is used in every analysis. The effect of pressure correction with the time constant 4 ms was examined in 5 healthy and 5 diseased infants. The same breaths were calculated with and without pressure correction. The influence of the pressure correction on compliance and resistance was however small implying an average error in R and C of less than 5%. This error was accepted and no pressure compensation was performed in the series presented in the following sections.

Calculations

As was pointed out in a preceding chapter relating the output (flow) to the input (pressure) signal by division provides information on the flow achieved for a certain driving pressure. If the computations are performed over a series of cycles the ratio can be representative for the yield of the system in terms of flow for a certain mean muscular force applied to the system during breathing. The information contained in this ratio is independent of any specific theoretical lung model or condition applied and has a direct physiological significance. Assuming ventilatory muscle force to be active during inspiration only, an expression for such a flow-pressure ratio, or admittance for the ventilatory system is

$$B = \frac{\int_0^{T_I} \dot{V}dt}{\int_0^{T_I} P_{pl}dt}$$

where B is the admittance V is flow P_{pl} transpulmonary pressure and T_I time for an inspiration.

The ratio B can most simply be calculated by the computer as $B = \Sigma V/\Sigma P_{pl}$ during inspiration. In the clinical study to be presented below B was calculated by hand from mean values of variables of the study under the assumption that

$$B = \frac{\bar{V}_{in}}{\bar{P}_{pl}} \approx \frac{2\bar{V}_T}{\bar{P}_{max(in)}\ \bar{T}_{in}} \qquad (24)$$

$\bar{V}_{in}$ = the mean inspiratory flow, $\bar{V}_T$ the mean tidal volume, $\bar{T}_{in}$ the mean time for inspiration for the breaths in the study and $P_{max(in)}$ is the mean pressure difference between the onset of inspiration and the lowest P_{pl} recorded.

A breath may be defined as the volume change between two consecutive points of time when $V = 0$ and $\dot{V}<0$ assigning the negative sign to inspiratory flows. A breath may be divided into an inspiratory phase ($V<0$) and an expiratory phase ($V>0$). In a preceding section it was shown that body volume variations V_{TG} during breathing are not in phase with air flow V_{aw}. A breath may thus be defined from either V_{TG} or V_{aw} having somewhat different meaning. To use V_{aw} is adequate when ventilation and gas exchange is studied. In the same way V_{TG} is of value from certain mechanical points of view. In the mathematical lung model presented on page

$$P(t) = \frac{1}{C}\int_0 Vdt + RV$$

V is not strictly defined in this respect. Generally the equation is used and parameters calculated with $V = V_{aw}$ or V_{TG}, without, as will be demonstrated, significantly differing results. If,

however the parameters C and the components of R, i.e. lung tissue resistance R_{lt} and airway resistance R_{aw} are linearly related to their adequate variables (see below) in the volume, pressure and flow range of a breath, the flow measured and used for the calculations will affect the parameters under certain circumstances. The elastic pressure component is proportional to the volume change of the lung ΔV_{TG} and the resistive component may be separated into two components, one proportional to air flow $R_{aw}\ \dot{V}_{aw}$ representing pressure drop due to air flow resistance and another proportional to lung-volume change $R_{lt}\ \dot{V}_{TG}$, representing pressure absorbed by lung tissue resistance to motion.

This means that

$$P(t) = \frac{1}{C}\Delta V_{TG} + R_{aw}\ \dot{V}_{aw} + R_{lt}\ \dot{V}_{TG}.$$

But $\dot{V}_{aw} = \dot{V}_{TG} - K_{aw}\ddot{V}_{aw}$ according to equation 14. Now

$$P(t) = \frac{1}{C}\Delta V_{TG} + R_{aw}\dot{V}_{TG} - R_{aw}K_{aw}\ddot{V}_{aw} +$$

$$+ R_{lt}\dot{V}_{TG}.$$

But lung resistance R_l is defined as

$$R_l = R_{aw} + R_{lt}$$

Then

$$P(t) = \frac{1}{C}\Delta V_{TG} + R_l\dot{V}_{TG} - R_{aw}K_{aw}\ddot{V}_{aw} \quad (25)$$

with the significance that if V in equation 2 is replaced by V_{TG} a term in the equation is overlooked diminishing the reliability of the model. As $K_{aw} = R_{aw}V_{TG}/P_{BD}$ this error term is

$$-(R_{aw})^2\frac{V_{TG}}{P_{BD}}\ \ddot{V}_{aw} = \alpha, \text{ defining } \alpha.$$

P_{BD} is barometric pressure minus water vapor pressure.

In a similar way it can be shown that if V in equation 2 is replaced by V_{aw},

$$P(t) = \frac{1}{C}\Delta V_{aw} + (R_l + \frac{R_{aw}\ V_{TG}}{C\ P_{BD}})\ \dot{V}_{aw} +$$

$$+ \frac{V_{TG}}{P_{BD}}\ R_{aw}R_{lt}\ddot{V}_{aw} \quad (26)$$

In addition to a similar error term

$$\beta = \frac{V_{TG}}{P_{BD}}R_{aw}\ R_{lt}\ddot{V}_{aw}$$

It can be seen that there are differences in tidal volumes with consequences for the value of C and in the parameter for $\dot{V}$ in expression 25 and 26.

The quantitative aspects of the errors are presented in Table 6. The parameter errors introduced by not considering α or β will mainly affect C. It can be concluded that as long as R_{aw} and V_{TG} are not much increased the errors involved are very small but increase rapidly when the critical parameters increase. In the most unfavourable situation, illustrated in Table 6 by a newborn infant with severe airway obstruction together with high lung volume and high maximal volume acceleration, the error in the pressure difference between the beginning and the end of an inspiration is very high. The advantage in calculation of lung compliance using the body plethysmograph to record the true volume change is hence lost due to the error in pressure determination caused by the plethysmographic recording of flow. In infants with this combination of factors affecting a calculation of lung compliance with this method should be avoided. In the material of newborn infants with pulmonary disease to be described in next section the calculated error in compliance is small (Table 7). In healthy infants during quiet breathing the error in lung compliance calculated from Table 6 is less than 5 %. In the groups of healthy and diseased infants studied these errors were accepted. Errors in V_T and R when V_{aw} is measured and used in the equation are negligible in the conditions studied.

Airway resistance is shown in adults to be related to lung volume and flow (18). This means that lung resistance changes during a breath. Changes in the lumina of airways, bronchomuscular tone or mucosa cause variations in R. The recoil of the lung is volume dependent and may change during a breath, which may cause lung

Table 6. Errors in calculations according to the assumptions given in the text.

Infant group	If $\dot{V} \approx \dot{V}_{TG}$				If $\dot{V} \approx \dot{V}_{aw}$		
	max $\ddot{V}$ l/s^2	α, cmH_2O	Error in ΔP_{pl}, cmH_2O	β, cmH_2O	Error in ΔP_{pl}, cmH_2O	Error in R, $cmH_2O/(l/s)$	Difference in V_T ml
Healthy	0.5	$3.7 \cdot 10^{-2}$	0.07	$1.6 \cdot 10^{-2}$	−0.03	0.7	<0.01
IRDS	1.2	$1.5 \cdot 10^{-1}$	0.30	$3.4 \cdot 10^{-2}$	−0.07	2.7	<0.01
Aspiration syndrome	1.0	$8.8 \cdot 10^{-2}$	0.17	$3.3 \cdot 10^{-2}$	−0.07	1.9	<0.01
Unclassified disorders	1.0	$1.9 \cdot 10^{-1}$	0.38	$5.6 \cdot 10^{-2}$	−0.11	1.3	<0.1
Airway obstruction	1.5	2.9	5.8	0.27	−0.54	3.8	0.3

Groups are identical to those in table 2 giving basic values for the calculations performed. Values of lung compliance for calculation of error in R are from section III. ΔP_{pl} is the difference in pleural pressure between end-expiration and end inspiration. Positive sign of error in ΔP_{pl} implies an overestimation.

Table 7 Errors in calculated compliance due to the influence of airway resistance thoracic gas volume and volume acceleration on recorded flow Patient groups according to section *III*

	Healthy infants	IRDS	Aspiration syndrome	Unclassified disorders
Average error in C	< 5 %	< 5 %	< 5 %	≈ 10 %
Max. error observed	11 %	30 %	17 %	27 %
in ml/cmH$_2$O	0.4	0.3	0.2	1.3
patient number in appendix		3	22	32

compliance to vary within one breath. Changes in amounts of blood and lymph in the lung during the breathing cycle may influence both parameters. In cases of different time constants within the lung, R as well as C *are expected to vary (40).* Beside such biological variations in the relations between the variables in the lung model, the well-known influence of heart action on esophageal pressure registration and mechanical or electrical noise are other sources of such variation The influence of different types of uncorrelated variation on the parameters may be minimized and averaged by algebraic methods.

During breathing P and V is sampled at high frequency by the computer at the same moment and the corresponding V *is calculated continuously* To exclude the influences of the absolute values of P and V on further calculations, pressure and volume in every sample are expressed as deviations from their means during the breath according to our lung model, in every sample

$$P - \bar{P} = \frac{1}{C}(V - \bar{V}) + R\dot{V} + e \quad \text{or}$$

$$\Delta P_d = \frac{1}{C}\,\Delta V_d + R\dot{V} + e$$

where e is the sum of errors of all types interfering with the system and the model. After arranging and squaring, summation gives

$$\Sigma\left(P_d - \frac{1}{C}V_d - R\dot{V}\right)^2 = \Sigma e^2 \tag{27}$$

This expression constitutes the lung model used and defines R and C. Minimal sum of squared errors can be found after differentiating in respect to C and R respectively and these parameters can be determined from the expression

$$R = \frac{\Sigma VP_d - \frac{1}{C}\Sigma V_d V}{\Sigma V^2}$$

$$C = \frac{\Sigma V_d^2}{\Sigma V_d P_d - R\Sigma V_d V}$$

Calculations can be made over a whole breath as well as over only a part of it. The effect of errors is averaged over the period analyzed. This means that the influence of uncorrelated errors as noise and – usually – deflections caused by heart activity will diminish and changes in airways and parenchyma will be averaged to a level dependent on the relative length of the sampling period.

With this method of calculation sampling errors involved in common graphical methods are excluded, variations in the constancy of the parameters are considered and averaged and an advantageous adaptation of the method of registration to the lung model is created.

Standard calculations.

Resistance was calculated during inspiration, expiration and over the whole breath. To avoid possible errors due to nonlinearity in parameter C only the average resistance over the whole breath was used in the clinical study

Compliance was calculated over inspiration only as resistance was assumed not to vary significantly during inspiration and a constant R is a prerequisite for reliable calculations.

The computer program.

Selection of breaths for the analysis and calculations of parameters are done on a (digital) minicomputer PDP 12 The program is designed to work in real time with branching and direction faculties through operator interactions. The parameter program works mainly in four modes. The calibration mode allows one to supply static calibration signals for pressure and flow The calibration signals are displayed and the calibration values calculated from the mean of the 128 sample points displayed when accepting the signal by pressing a key The flow-zero signal is later used to determine a breath.

The input mode selects a breath from the flow signal. The flow is then already corrected according to equation 17 as described on page 12. A breath is selected as an interval between two consecutive points of zero flow with negative derivative. A hysteresis function avoids spurious zero values to determine the end of a breath. A breath must contain between 128 to 256 sample points to be accepted, if not the program automatically searches for the next breath. Every rejected breath is signalled. The samling rate can easily be changed at any time A fixed sampling rate is inappropriate since the length of a breath varies considerably from infant to infant. The selected breath is immediately displayed as a pressure-flow loop a pressure-volume loop or a diagram of flow volume and pressure versus time.

If the breath is accepted by the operator the program enters the calculation mode. The calculated parameters are printed out and/or stored for statistical analysis. The intermediate result in the calculations are also stored, i.e. means variances and co-variances of the three variables, flow volume and pressure, calculated over each fourth of the breath. As an option the whole breath can be stored on tape or disc.

The fourth mode of the program is the statistical part. This part allows calculation of the basic statistical parameters from the stored parameters. *Selection of breaths.* Every breath presented on the screen was judged before acceptance by the following criteria. To be accepted as a breath, the volumes inspired and expired must not differ by more than 10 % to avoid inaccuracies in the calculations, and, to avoid errors due to peristaltic waves, differences between the first and last pressure recorded during the breath are accepted only if the pressure-volume loop is not closed and only if the start and end pressures can be regarded as points on a hypothetical static pressure-volume diagram ('compliance line') of the breath. There was no selection in respect to tidal volume breath length, or conformation of the diagrams displayed, except concerning pure recording artefacts due to noise from the recording instruments.

The accuracy of the computations was tested by checking of the volume calculations. First the accuracy of the flow-recording system and the integrator was tested. Flow and volume calibra-

tions were performed as described on page 11 using standard flows. A syringe was thereafter connected to the pneumotachograph via a wide tube and 10 0 ml of air was given repeatedly through the system. The corresponding deflections were calculated to be 9 86 ml ± 0 ml (5 determinations) with a measuring uncertainty of ± 0.18 ml. The free opening in the plethysmograph was then tightened and a syringe was connected to a canula through the wall of the box and a volume of 11 8 ml air was forced in and out and the volume was calculated by the computer after compensation with time constant as described. The mean volume was calculated to be 11.6 ml, with a standard error of the mean of 0 11 ml. The difference is not significant.

Validity of the lung model. Effects of non-linearity

The method described above is very similar to a multiple regression analysis. It should be emphasized, however that these similarities must not be used for extended interpretations of the results. The errors in multiple regression analysis are assumed to be independent and uncorrelated and this is certainly not true for the errors in our model. If there is a large error in our model fit at one sampling moment it is very likely that it is large also at the next moment. For instance if the heart is disturbing the pressure recording the errors will be correlated to the heart cycle and be a continous function of time. From a statistical point of view the correlated residuals cause the parameter estimates to be biased. There are ways to avoid this bias (5) but then it is no longer possible to work in real time with the computer facilities we have. The errors introduced are significant if one wishes to calculate the best parameter for a specific breath but become insignificant when calculating the best average parameters for a specific baby since the variations from breath to breath are large.

Because of the correlated residuals it is not possible to use a simple technique to test whether the order of the model is sufficient or not. Maximum-likelihood estimates (26) of the model order show that R and C are sufficient parameters to describe the system when there is no obvious nonlinearity in the loop Details will be published elsewhere

The expiratory phase in a grunting baby is not well described by the model. This was expected, as the resistance during grunting is extremely variable, judging from the flow registration. Another and remarkable exception is registrations from several cases of acute idiopathic respiratory distress syndrome (IRDS) The volume-pressure diagrams in these infants show a bent and narrow loop (page 43) It is already obvious from this diagram that such a pattern is not compatible with a concept of constant C and/or R in the model. It may represent a change in the elastic properties of the parenchyma, in resistivity in flow distribution or in any combination of such factors and may be an expression of mechanical lung derangement typical for IRDS

Identification and description of non-linearity

The loop pattern with obvious non-linearity is not identified by the standard calculations performed. To identify and describe this phenomenon two values of compliance were calculated by equation 27 during inspiration, one from flow and pressure observations up to half the tidal volume C_1 and one from this point up to full tidal volume C_2 As will be shown in a later section there was a significant difference in the ratio C_1/C_2 between healthy infants and infants with IRDS and aspiration syndrome It must however be emphasized that dissimilarities in C_1 and C_2 indicating non-linear parameters, do not necessarily imply non-linearity in parameter C Because of the demonstrated usefulness of these separate compliance values they were included in the standard calculations.

The physiological significance of the mechanical parameters.

R and C are defined from the lung model (equation 27) and the mode of their calculation and may be regarded as regressions of esophageal pressure on flow and volume respectively during the period of a breath selected for study

R relates the flow-dependent variations in pressure to flow and is thereby a measure of the resistance of the lung to flow during the period studied and determines the part of the pressure doing irreversible work on the lung. Parameter C relates in the same way the volume variations to

the corresponding pressure variation, and determines the part of the pressure doing reversible work on the lung. Under static conditions, when V and $\dot{V}$ equals zero C is determined by the static recoil of the lung at the actual lung volume. Accepting the lung model presented above, C, under dynamic conditions, looses its absolute dependence upon lung elasticity and is affected by differences in the time constants within the parenchyma (40). R is also affected by those factors not included in the model. In healthy adults (40) and infants (43 49) these phenomena seem to be of little importance and Wohl et al. (49) did not find frequency-dependent R in healthy newborns. In diseased lungs, however as shown in adults (25) the parameters may be frequency dependent. Because of this R and C measured during breathing are functions of lung mechanics in a broader sense than of resistance to air flow and of lung elasticity alone. The relative influence of other factors may be difficult to determine. This means that the physiological meaning of the parameters may change with individuals and types of disease

The result may have a clinical significance more as a pattern that can be interpreted by experience from mechanical examinations on infants with different forms of pulmonary disease than as a description of the elastic and resistive status of the organ of ventilation. Information on unsatisfactory model adaptation can be clinically useful as it implies information on altered mechanical function of the lung. This information can be extracted in a semi-quantitative way by the method described.

Closing remarks

The development of this system for measurement of mechanics of breathing in severely diseased infants have implied compromises between practical and theoretical requirements. With the system described healthy as well as diseased newborn infants have been examined without hazards. To attain this we have accepted relatively large time constants in the systems for measurement of flow and pressure As has been shown these error may be compensated for and this has been done concerning flow The error in pressure however, was small in the studies performed and was accepted. Another error in the pressure signal used for calculations is due to the difference between the flow measured by the plethysmograph, and the corresponding flow in the airways. As demonstrated also this source of error was small in the material examined and was accepted. With the method of calculation used the influence of factors uncorrelated to the model are minimized and all relevant information in the signals is exploited for calculation of the parameters. A computer is necessary and is an outstanding tool for calculations of this kind. The fast production of results makes a clinical adaption of the method possible

There are many reasons to believe that a lung model that describes ventilation in healthy lungs well will do so less well in diseased lungs. If the impedance to breathing is unequal in different parts of the organ the parameters will be frequency dependent, and this property is not considered in the model. Failure of the model is also to be expected if the volume of the lung is changed in steps, as happens if parts of the airways are closed or opened up during breathing, and the same effect is seen if processes in the parenchyma add plastic properties to the lung or make elastic or resistive properties markedly non-linear in respect to volume or flow In this study the model adaptation was not good in some cases of IRDS and in grunting. In less extreme cases with lung diseases, however the model worked well.

References.

1. Abt, cited by Engel, S. in Engel, S., *The Child' Lung* Ed ard Arnold & Co, London, 1947 p. 1
2. Agostoni, E Mechanics of the pleural space. *Physiol Rev* 2:57 1972.
3. Agostoni, E and Miserocchi, G Vertical gradient of transpulmonary pressure with active and artificial lung expansion. *J Appl Physiol*, 29:705 1970
4. Ainsworth, M. and Eveleigh, J W A method of estimating lung air-way resistance in humans. Ministry of Supply Chem. Defence Exptl. Estab. *Porton Tech Paper* 320 1952.
5. Aström, K.J and Eykhoff, P System identification – survey *Automatica*, 7 123 1971
6. Auld, P A.M., Nelson, N.M Cherry R.B Rudolph, A.J & Smith, C.A.. Measurement of thoracic gas volume in the newborn infant. *J Clin Invest* 42.476 1963

7 Avery M.E.. *The lung and its disorders in the newborn infant* Saunders. 2nd edition, 1968, p. 63.

8. Banchero, N., Schwartz, P E. Tsakiris, A.G & Wood, E.. Pleural and esophageal pressures in the upright positi n. *J Appl Physiol*, 23.228 1967

9 Bargeton, D and Barres, G Time characteristics and frequency response of body plethysmograph. *In Body Plethysmography* edited by A.B. DuBois and K.P van de Woestijne, Karger Basel, 1969 p. 2

10. Campbell, E.J.M Agostoni, E. & Newsom Davis, J *The respiratory muscles.* Lloyd-Luke Ltd, London, 2nd ed., 1970.

11 Chu, J Dawson, P Klaus, M & Sweet, A.. Lung compliance and lung volume measured concurrently in normal full-term and premature infants. *Pediatrics*, 34.525 1964

12. Chu, J., Clements, J.A Cotton, E.K., Klaus, M.H., Sweet, A.Y & Tooley W.H.. Neonatal pulmonary ischemia. Part I Clinical and physiological studies. *Pediatrics*, 40.709 1967

13 Cook, C.D., Cherry R.B., O'Brien, D Karlberg, P & Smith, C.A. Studies of respiratory physiology in the newborn infant. I. Observations on normal premature and full-term infants. *J Clin Invest* 34.975 1955

14 Cross, K.W The respiratory rate and ventilation in the newborn baby *J Physiol*, 109 459 1949

15 Deming, J & Washburn, A.. Respiration in infancy *Am J Dis Child*, 49.108 1935

16. Dinwiddie, R. and Russel, G. Relationship of intrae sophageal pressure to intrapleural pressure in the newborn. *J Appl Physiol*, 33 415 1972.

17 Drorbaugh, J.E., Segal, S., Sutherland, J.M., Oppé, T E., Cherry R.B. & Smith, C.A. Compliance f lung during first week f life. *Am J Dis Child*, 105:63 (1963).

18. DuBois, A.B. Resistance t breathing. In. *Handbook of physiology* Section 3, edited by W.O. Fenn and H. Rahn, Respiration, vol 1 1964 p. 451

19 DuBois, A.B., Brody A.W Lewis, D.H & Burgess Jr, B.F Oscillation mechanics of lungs and chest in man. *J Appl Physiol*, 8:587 1956

20. DuBois, A.B Botelho, S.Y Bedell, G.N Marshall, R. & Comroe Jr, J.H. A rapid plethysmographic method for measuring thoracic gas volume: comparison with nitrogen washout method for measuring functional residual capacity in normal subjects. *J clin Invest*, 35.322, 1956.

21 Engel, S. *The child's lung* Edward Arnold & Co London, 1947

22. Ferris, B., Mead, J & Frank, R Effect of body position on esophageal pressure and measurement of pulmonary compliance. *J Appl Physiol*, 14:521, 1959

23 Geubelle, F Karlberg, P Koch, G., Lind, J Wallgren, G. & Wegelius, C. L aération du poumon chez le nouveau-né. *Biol Neonat* 1.169 1959

24 Geubelle, F & Senterre. J Methods of investigation of the mechanics of breathing in the artificially ventilated newborn. *Biol Neonate* 16.35 1970

25 Grimby G., Takishima, T Graham, W Macklem, P & Mead, J Frequency dependence f flow resistance in patients with obstructive lung disease. *J Clin Invest* 47.1455 1968.

26. Gustavsson, L.. Parametric identification of multiple input, single output linear dynamic systems. Report 6907 1969 Lund Institute of Technology Div of automatic control.

27 Hardt, von der, H. & Geubelle F Relationship between endoesophageal and intrathoracic pressure in children. *Respiration* 30:252, 1973.

28. Karlberg, P Cherry R.B. Escardo, F & Koch, G.. Respiratory studies in newborn infants. I. Apparatus and method for studies of pulmonary ventilation and the mechanics f breathing. Principles f analysis in mechanics of breathing. *Acta Paediat* 49.345 1960

29 Klaus, M., Tooley W.H., Weaver, K.H. & Clements, J.A. Lung volume in the newborn infant. *Pediatrics*, 30.111 1962.

30. Knowles, J.H Hong, S.K. & Rahn, H Possible errors using esophageal balloon in determination f pressure-volume characteristics of the lung and thoracic cage. *J Appl Physiol*, 14:525 1959

31 McMahon, S.M., Proctor D.F & Permutt, S.. Pleural surface pressure in dogs. *J Appl Physiol*, 27:881 1969

32. Mead, J & Gaensler E.A.. Esophageal and pleural pressure in man, upright and supine *J Appl Physiol*, 14 81 1959

33 Mead, J. Measurement f inertia of the lungs at increased ambient pressure. *J Appl Physiol*, 9.208 1956.

34 Mead, J Mechanical properties f lungs. *Physiol Rev* 41.281 1961

35. Mead, J & Agostoni, E. Dynamics of breathing *In Handbook of physiology* section 3 ed. Fenn, W O. & Rahn, H. Respiration, vol. 1 1964 p. 411

36. Milic-Emili, J & Petit, J.M.. Relationship between endoesophageal and intrathoracic pressure variations in dog. *J Appl Physiol*, 14:535 1959

37 Milic-Emili, J Mead, J & Turner, J.M Topography of esophageal pressure as a function of posture in man. *J Appl Physiol*, 19.212, 1964

38. Nolte, D.. Experimental studies on the existence of isothermal conditions in the human lung. *In Body plethysmography* Edited by A.B. DuBois and K.P van de Woestijne, Karger, Basel, 1969 p. 102.

39 Olsson, T & Victorin, L. Transthoracic impedance, with special reference to newborn infants and the ratio air-to-fluid in the lungs. *Acta Paediat Scand* Suppl 207 1970

40. Otis, A.B McKerrow C.B., Bartlett, R.A., Mead J., McIlroy M.B., Selverstone, N.J & Radford E.P Mechanical factors in distribution of pulmonary ventilation. *J Appl Physiol*, 8 427 1956.

41. Petit, J.M. & Milic-Emili, G. Measurement f endoesophageal pressure. *J Appl Physiol*, 13 481 1958

42. Polgar G. & Lacourt, G., A method for measuring respiratory mechanics in small newborn (premature) infants. *J Appl physiol*, 32:555 1972.

43 Reynolds, R. & Etsten, B.E., Mechanics of respiration in apneic anesthetized infants. *Anesthesiology* 27 13 1966.

44 Rohrer, F Physiologie der Atembewegung. *In Handbuch der normalen und pathologischen Physiologie* ed. A.T.J Bethe et al. Springer, Berlin 1925 Vol. 2, p. 70

45 Serterre, J. & Geubelle, F Measurement of oesophageal pressure in the newborn. *Biol Neonate* 16 47 1970.

46. Skoogh, B.E. & Ritzell, S., A high frequency response volume displacement body plethysmograph. *Scand J clin Lab Invest*, 31 419 1973

47 Stanescu, D.C., DeSutter, P & Woestijne, K.P van de Pressure-corrected flow body plethysmograph. *Amer Rev Resp Dis*, 105 304 197_

48. Swyer, P.R., Reiman, R.C. & Wright, J.J., Ventilation and ventilatory mechanics in the newborn. *J Pediat*, 56 612, 1960

49 Wohl, M.E.B., Stigol, L.C. & Mead, J Resistance of the total respiratory system in healthy infants and infants with bronchiolitis. *Pediatrics*, 43 495 1969

7 Avery M.E. *The lung and its disorders in the newborn infant* Saunders, 2nd edition, 1968, p. 63.

8. Banchero, N., Schwartz, P.E., Tsakiris, A.G. & Wood, E. Pleural and esophageal pressures in the upright position. *J Appl Physiol*, 23:228, 1967

9 Bargeton, D and Barres, G Time characteristics and frequency response of body plethysmograph. *In Body Plethysmography* edited by A.B DuBois and K.P van de Woestijne, Karger Basel, 1969 p. 2.

10. Campbell, E.J.M Agostoni, E & Newsom Davis, J *The respiratory muscles* Lloyd Luke Ltd, London, 2nd ed 1970.

11 Chu, J., Dawson, P., Klaus, M. & Sweet, A. Lung compliance and lung volume measured concurrently in normal full-term and premature infants. *Pediatrics*, 34:525 1964

12. Chu J., Clements, J.A., Cotton, E.K., Klaus, M.H., Sweet, A.Y & Tooley W.H., Neonatal pulmonary ischemia. Part I Clinical and physiological studies. *Pediatrics*, 40 709 1967

13. Cook, C.D., Cherry R.B., O'Brien, D Karlberg, P & Smith, C.A., Studies of respiratory physiology in the newborn infant. I Observations on normal premature and full-term infants. *J Clin I nvest* 34:975, 1955

14 Cross, K.W The respiratory rat and ventilation in the newborn baby *J Physiol*, 109 459 1949

15 Deming, J & Washburn, A. Respiration in infancy *Am J Dis Child*, 49 108 1935

16. Dunwiddie, R. and Russel, G. Relationship of intraesophageal pressure to intrapleural pressure in the newborn. *J Appl Physiol*, 33 415 1972.

17 Drorbaugh, J.E. Segal, S., Sutherland, J.M Oppé, T.E., Cherry R.B. & Smith, C.A. Compliance of lung during first week of life. *Am J Dis Child*, 105:63 (1963).

18. DuBois, A.B Resistance to breathing. *In Handbook of physiology* Section 3 edited by W O. Fenn and H. Rahn, Respiration, vol 1 1964 p. 451

19. DuBois, A.B Brody A.W Lewis, D.H & Burgess Jr, B.F Oscillation mechanics of lungs and chest in man. *J Appl Physiol*, 8:587 1956

20. DuBois, A.B., Botelho, S.Y Bedell, G.N Marshall, R. & Comroe Jr, J.H. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *J clin Invest*, 35:322, 1956

21 Engel, S. *The child's lung* Edward Arnold & Co London, 1947

22. Ferris, B., Mead, J & Frank, R. Effect of body position on esophageal pressure and measurement of pulmonary compliance. *J Appl Physiol*, 14:521, 1959

23 Geubelle, F., Karlberg, P Koch, G Lind, J., Wallgren, G & Wegelius, C. L aération du poumon chez le nouveau-né. *Biol Neonat* 1:169 1959

24 Geubelle, F & Senterre, J Methods of investigation of the mechanics of breathing in the artificially ventilated newborn. *Biol Neonate* 16 35 1970.

25 Grimby G., Takishima, T., Graham, W Macklem, P & Mead, J Frequency dependence of flow resistance in patients with obstructive lung disease. *J Clin Invest* 47:1455, 1968.

26 Gustavsson, L. Parametric identification of multiple input, single output linear dynamic systems. Report 6907 1969 Lund Institute of Technology Div. of automatic control.

27 Hardt, von der H. & Geubelle, F Relationship between endoesophageal and intrathoracic pressure in children. *Respiration*, 30 [illegible] 1973.

28. Karlberg, P Cherry R.B., Escardo, F & Koch, G. Respiratory studies in newborn infants. I. Apparatus and methods for studies of pulmonary ventilation and the mechanics of breathing. Principles of analysis in mechanics of breathing. *Acta Paediat*, 49:345 1960.

29 Klaus, M., Tooley W.H., Weaver, K.H. & Clements, J.A. Lung volume in the newborn infant. *Pediatrics*, 30:111 1962

30. Knowles, J.H Hong, S.K. & Rahn, H Possible errors using esophageal balloon in determination of pressure-volume characteristics of the lung and thoracic cage. *J Appl Physiol*, 14:525, 1959

31. McMahon, S.M., Proctor D.F & Permutt, S Pleural surface pressure in dogs. *J Appl Physiol*, 27:881 1969

32. Mead, J. & Gaensler E.A., Esophageal and pleural pressure in man, upright and supine. *J Appl Physiol*, 14:81 1959

33 Mead, J., Measurement of inertia of the lungs at increased ambient pressure. *J Appl Physiol*, 9:208 1956.

34 Mead, J Mechanical properties of lungs. *Physiol Rev* 41:281 1961

35. Mead, J & Agostoni, E. Dynamics of breathing *In Handbook of physiology* section 3 ed., Fenn, W O & Rahn, H. Respiration, vol. 1 1964 p. 411.

36. Milic-Emili, G & Petit, J.M.. Relationship between endoesophageal and intrathoracic pressure variations in dog. *J Appl Physiol*, 14:535 1959

37 Milic-Emili, J Mead J & Turner J.M. Topography of esophageal pressure as a function of posture in man. *J Appl Physiol*, 19:212, 1964

38. Nolte D. Experimental studies on the existence of isothermal conditions in the human lung. *In Body plethysmography* Edited by A.B. DuBois and K.P van de Woestijne Karger, Basel, 1969 p. 102.

39. Olsson, T & Victorin, L.. Transthoracic impedance, with special reference to newborn infants and the ratio air-to-fluid in the lungs. *Acta Paediat Scand* Suppl 207 1970.

40. Otis, A.B., McKerrow C.B Bartlett, R.A., Mead, J., McIlroy M.B., Selverstone, N.J. & Radford, E.P Mechanical factors in distribution of pulmonary ventilation. *J Appl Physiol*, 8:427 1956.

41 Petit, J.M. & Milic-Emili, G. Measurement of endoesophageal pressure. *J Appl Physiol*, 13:481 1958.

42. Polgar G. & Lacourt, G.. A method for measuring respiratory mechanics in small newborn (premature) infants. *J Appl physiol*, 32:555 1972.

43 Reynolds, R. & Etten, B E. Mechanics of respiration in apneic anesthetized Infants. *Anesthesiology* 27 13 1966.

44 Rohrer F Physiologie der Atembewegung. *In Handbuch der normalen und pathologischen Physiologie* ed. A T J Bethe et al. Springer, Berlin 1925 Vol. 2, p. 70.

45. Senterre, J. & Geubelle, F Measurement of endoesophageal pressure in the newborns, *Biol Neonate*, 16:47 1970.

46. Skough B.E. & Rizell, S.. A high frequency response volume displacement body plethysmograph. *Scand J clin Lab Invest*, 31:419 1973.

47 Stanescu D C., DeSutter P & Woestijne K.P van de: Pressure-corrected flow body plethysmograph. *Amer Rev Resp Dis*, 105:304 1972.

48. Swyer P.R., Reiman, R.C. & Wright, J.J.. Ventilation and ventilatory mechanics in the new born, *J Pediat*, 56:612, 1960.

49 Wohl, M E.B Stigol, L.C. & Mead, J Resistance of the total respiratory system in healthy infants and infants with bronchiolitis. *Pediatrics*, 43:495 1969

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III MECHANICAL AND VENTILATORY PARAMETERS IN HEALTHY AND DISEASED NEWBORN INFANTS

Ola Hjalmarson and Torsten Olsson

Introduction

Neonatal pulmonary disease is a major clinical problem. Different pathogenetic patterns present themselves in a rather uniform clinical picture with increased respiratory frequency cyanosis, retractions and often "grunting" breathing, often referred to as "respiratory distress" Increasing knowledge of radiology pathology physiology and the clinical course in this syndrome has led to a differentiation in diagnoses Idiopathic respiratory distress syndrome (IRDS) or hyaline membrane disease (HMD) (39) and aspiration syndrome (34 40) or type II respiratory distress syndrome (37 43) are dominant but other lung disease, congenital lung malformations and heart diseases often appear with similar symtoms. Clinical respiratory disturbances may also originate from delayed functional adaptation immediately after birth and from disturbances of the central nervous system.

A great deal of controversy exists about clinical diagnostic criteria in neonatal pulmonary disease The main diagnostic methods used are lung X-ray estimation of the degree of right to-left shunt, determination of acid-base status and physical status. Pulmonary function testing has had no place in routine diagnostic work in neonates with pulmonary disease because of the lack of suitable methods. However as described in the preceding paper it is possible to analyse the pulmonary mechanics in a neonate without requiring any cooperation of the patient. Analysis of pulmonary mechanics in the neonates is of special interest as one factor of considerable importance in the pathogenesis of IRDS is considered to be an interference with the formation of surfactant (17) with consequences for the mechanical properties of the lung. It has also been shown that IRDS infants have low pulmonary compliance (10 37).

Aim of the study

The aim of the study was to evaluate mechanical lung parameters as diagnostic tools in neonatal pulmonary disease This was accomplished by studying pulmonary compliance and resistance togheter with various parameters of ventilation in a group of newborn infants with pulmonary disease and relating the results to radiological findings, oxygen requirements clinical diagnosis and to mechanical and ventilatory parameters in a reference group of healthy newborns.

Material

Thirty-six newborn infants with signs of pulmonary disease were studied together with a reference material of healthy newborn infants The diseased infants were selected by the following criteria

1) newborn infant with signs of respiratory disease appearing during the first day of life with
2) breathing frequency above 60/minute for at least one hour or cyanosis while breathing room air
3) pathological lung roentgenogram, and
4) absence of congenital vitium.

(Infants with signs of patent ductus arteriosus, appearing during the disease, have been included).

Of the diseased infants 2 died and 34 recovered. Details are presented in the Appendix.

The reference group consisted of 49 newborn infants born during the same period of time as the sick infants without clinical signs of any disease Birth weights were 1310–4750 grams. The mothers had provided informed consent for the studies.

Methods.

Lung mechanics, ventilation and thoracic gas volume (V_{TG}). These methods have been described in detail in the preceding section. All infants were studied naked or with napkins in a flow displacement body plethysmograph placed in an incubator (Isolette, Airshield Inc.). The temperature in the incubator was 32–34° and in the pletysmograph 32–36°. Intraesophageal pressures were measured with an esophageal balloon introduced through a nostril. Any desired oxygen concentration could be supplied to the infant during the study and cardiac rate and frequency of breathing were continously monitored in sick infants by an impedance plethysmograph (41). The infants were examined 1–3 hours after a meal and when quiet after 5–10 minutes of adaptation to the apparatus. Flow and pressure registrations were recorded on tape (Ampex) continously or for 5–15 minutes periods. V_{TG} was determined afterwards. Every study was finished by calibrations of pressure flow and volume.

Thirty-one of the forty-nine infants in the reference group were examined more than once, the first occasion being within the first two days of life. Some of the smaller infants were followed with studies during their first weeks. The number of observations per individual and age at examination are shown in Tables 1 and 2. The total number of examinations in this group was 86.

Table 1. Number of observations per healthy infant.

	Number of observations per healthy infant				
	1	2	3	4	5
Number of infants	18	27	2	1	1

The infants with pulmonary disease were when possible examined repeatedly during the course of the disease and after clinical recovery. The total number of examinations in this group was 1_7. In the results every sick infant is represented by the examination performed when the infant was near the peak of its disease as reflected by highest value of calculated right to left shunt or from clinical status. In addition 24 of the sick infants were studied on the following recovery as defined by the first registration made after clinical status was normalized and after the infant had begun to gain in weight. All calculations were made by computer (PDP 1?) off line. The parameters caclulated appear in Table 3. Dynamic lung compliance and resistance were determined for every accepted breath (see section II page 21) from sampted pressure and flow values by least square adaptation to the lung model. Sixteen breaths were used for analysis.

In the following the terms compliance or C will be used to assign dynamic lung compliance.

Blood gas analysis. Blood samples were drawn from a catheter placed through an umbilical artery with its tip in abdominal aorta below the renal arteries. In 13 of the cases the artery was not catheterized and in these cases umbilical vein blood, arterialized capillary blood or blood from the radial artery was used. The blood gas measurements presented were taken within one hour following completion of the physiological studies. P_{O_2}, P_{CO_2} and pH in the sample were determined immediately after sampling by conventional electrodes (Radiometer Corp.).

Measurements of oxygen concentration of the gas in the incubator was made by an oxygen analyser

Table 2. Age at examination in healthy and diseased infants.

Material	Age at examination in days							
	<0.5	0.6–0.9	1.0–1.9	2.0–3.9	4.0–[illegible]	7.0–13.9	14.0–20.9	> 21
Ref. group	12	7	18	13	6	15	8	7
Acute disease	15	4	13	4				
Recovered				1	6	8	7	

Table 3 Measured and calculated parameters with abbreviations and units.

Dynamic lung compliance	C	ml/cmH_2O
Lung resistance	R	$cmH_2O/(l/s)$
Tidal volume	V_T	ml
Total ventilation	V_E	ml/min
Maximal inspiratory flow	$maxV_{in}$	ml/s
Maximal expiratory flow	$maxV_{ex}$	ml/s
Thoracic gas volume	V_{TG}	ml
Lowest inspiratory esophageal pressure in relation to pressure at the onset of inspiration, positive sign	$maxP_{in}$	cmH_2O
Highest expiratory esophageal pressure in relation to pressure at the onset of inspiration	$maxP_{ex}$	cmH_2O
Frequency of breathing	f	min^{-1}
Ratio between compliance calculated during the first and the second half of inspiration	C_1/C_2	–
Oxygen fraction in inspired air	F_iO_2	%
Duration of oxygen therapy	$DurO_2$	days

(Beckman) The sampling probe was placed near the nostrils of the infant and measurements were made continously or at frequent intervals.

Right-to-left shunt was calculated for the purpose of description by the method of Gupta, Dahlenburg, and Davis (19) using their nomogram.

Physical examination was made immediately before every study of lung mechanics by the same examiner.

Measurement of body size. Body length was measured after birth and then once a week. The infant was weighed daily. As the regular weight loss during the first days after birth is not related to any reduction in lung volume or metabolic activity, the birth weight has been used in calculations as long as the actual body weight was lower than birth weight.

Chest X-ray in the sick infants was performed as often as was required clinically. No radiological examinations were done on the healthy infants. The X-rays comprised frontal and side projections and were performed in the neonatal unit.

All films have been examined by the same radiologist (Dr H. Larsson).

Calculation of results

Every study included at least 16 breaths and for every measured variable the mean, standard deviation, range and median value was calculated. Only in a few occasions due to a single deviating value there was a substantial difference between the mean and the median of a measured variable. In these occasions the studies were represented by the median values and in all others by the means.

The breathing frequency was calculated as $1/T \cdot 60$ where T is the mean time of a breath. The calculated frequency was checked against the frequency from the continuos paper recording as number of breaths per 60 sec. In a few registrations from healthy pre term infants with an irregular pattern of breathing there was a difference of more than 5 breaths per minute and in these cases the mean breathing frequency over one minute was used. The ventilation per minute was calculated as breathing frequency times mean tidal volume. All results were fed into a PDP 15 computer as means from every examination for statistical analysis. For selected groups of observations means, standard deviations, correlations matrices and constants in linear regressions were calculated. For tests of significance of differences between means of groups of observations, student's t test was used after F-test for equal

variances For tests of significance of differences of means from populations with different standard deviations the method of Cochran was used. (42) The standard deviation in each group of sick or healthy infants was calculated as

$$s = \sqrt{s_x^2 + \bar{s}_i^2}$$

where s_x is the standard deviation of the varible from the individuals in the group and $\bar{s}_i$ is the mean standard deviation of the mean of the variable in each member of the group The mechanical and ventilatory variables measured were subject to considerable variation both within and between individuals. Because of this all observations from all individuals in the reference group were used for description in terms of means, standard deviations, correlations and regression analysis. For testing of differences in measured variables between diseased and healthy infants reference values of healthy infants were calculated using only one observation per infant. In infants studied more than once the first observation made after the age of 12 hours was used These reference values appear in Table 5

Table 5 Reference values from healthy newborns.

Variable	Unit	Mean	S.D.
R	$\frac{cmH_2O}{l/s}$	46	17
C[1)]	$\frac{ml}{cmH_2O}$	3.3	1 1
V_T[1)]	ml	13 2	4 7
$maxP_{in}$	cmH_2O	5.3	1.5
$maxP_{ex}$	cmH_2O	1 4	0.8
$maxV_{in}$)	ml	48	14
$maxV_{ex}$	ml	41	13
f	min^{-1}	54	15
V_E[1)]	$\frac{ml}{min}$	670	250
V_{TG}	ml	87	25
Weight	g	2650	780
Length	cm	48	3 2
		49 (for V_{TG}	29)

[1)] Adjusted to 2 kg body weight, using the regression coefficient in table 4

Table 4 Observations in healthy newborn infants. Mean, S.D range, and relations to body size.

Variable	Unit	Mean	S.D.	Range	Coefficient of correlation length	length[3]	weight (w)	Eq of regression
R	$\frac{cmH_2O}{l/s}$	42	18	17–85	–.008	–.030	– 132	
C	$\frac{ml}{cmH_2O}$	3 7	1 1	1.6–6 3	.367	.380*	429*	$C=2.15+.58w\cdot10^{-3}$
V_T	ml	14 8	4 7	5.6–33	400*	418	402	$V_T=8.6+2.3w\cdot10^{-3}$
$maxP_{in}$	cmH_2O	5.4	1 4	2.8–9 7	.090	094	.010	
$maxP_{ex}$	cmH_2O	1 4	0.8	0.3–4 7	.205	.218( )	.219( )	
max $V_{(in)}$	$\frac{ml}{sec}$	55	[illegible]	[illegible] 109	.375	.388	383**	$maxV_{in}$ 36 7 $1w\cdot10^{-3}$
max $V_{(ex)}$	$\frac{ml}{sec}$	46	15	13 104	.376**	.390*	.349**	
Frequency	min^{-1}	57	[illegible]	24–115	.066	.058	.048	
Ventilation	$\frac{ml}{min}$	810	260	270–1440	476	485	461	$V_E=420+145w\cdot10^{-3}$
V_{TG}	ml	87	28	44 139	.299	.228	192	
Weight	g	2680	810	1310–4750				
Length	cm	48	3.3	40–54				
		86 (For V_{TG}, n	50)					

Table 3. Measured and calculated parameters with abbreviations and units.

Dynamic lung compliance	C	ml/cmH$_2$O
Lung resistance	R	cmH$_2$O/(l/)
Tidal volume	V_T	ml
Total ventilation	V_E	ml/min
Maximal inspiratory flow	maxV_{in}	ml/s
Maximal expiratory flow	ma V_{ex}	ml/s
Thoracic gas olume	V_{TG}	ml
Lowest inspiratory esophageal pressure in relation t pressure t the onset of inspiration, positive sign	maxP_{in}	cmH$_2$O
Highest expiratory esophageal pressure in relation t pressure t the onset of inspiration	maxP_{ex}	cmH$_2$O
Frequency of breathing	f	min^{-1}
Ratio between compliance calculated during the first and the second half of inspiration	C_1/C_2	–
Oxygen fraction in inspired air	F O$_2$	%
Duration f oxygen therapy	DurO$_2$	days

(Beckman). The sampling probe was placed near the nostrils of the infant and measurements were made continously or at frequent intervals.

Right-to-left shunt was calculated for the purpose of description by the method of Gupta, Dahlenburg, and Davis (19) using their nomogram.

Physical examination was made immediately before every study of lung mechanics by the same exa iner

Measurement of body size. Body length was measured after birth and then once a week. The infant was weighed daily As the regular weight loss during the first days after birth is not related to any reduction in lung volume or metabolic activity the birth weight has been used in calculations so long as the actual body weight was lower than birth weight.

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flow and ventilation and negatively to maximum pressure and breathing frequency. After adjustment of C for body weight using the regression equation in Table 4 the weak negative correlation with R diminishes. The correlation with thoracic gas volume is not significant. (Figure)

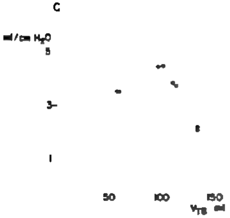

Fig. 2. Pulmonary compliance in healthy newborns in relation to thoracic gas volume.

The significant correlations were further studied in a multiple regression analysis describin compliance as a function of body weight w_{kg} in kg, tidal volume V_T in ml, maximal inspiratory flow V_{in} in ml/s, frequency f and pulmonary resistance R in $cmH_2O/(l/s)$

$$C = 1\ 73 + 0.254\ W_{kg} + 0..29\ V_T + + 0.009\ f - 0.034\ V_{in} - 0.015\ R. \quad (1)$$

The standard error of C was now 0.75 ml/ cmH_2O. The residuals were approximately normally distributed. The coefficient of regression for frequency did not significantly differ from 0. These regressions were responsible for 55 % of the variance of C in the sample

Pulmonary resistance R, showed no significant correlation to body size (Figure 3). The mean value was 42 $cmH_2O/(l/s)$, S.D 16 $cmH_2O/(l/s)$ and range 18–91 $cmH_2O/(l/s)$. The correlations

Table 8. Correlations between pulmonary compliance and other variables of ventilation before and after adjustment for body size.

	R	V_T	max P_{in}	max P_{ex}	max V_{in}	max V_{ex}	freq	V_E	V_{TG}
C	−.228	665	.265	034	375	159	281**	389	210
Adj C	− 190	.396	290*	066	232		334	238	

Table 9 Correlations between pulmonary resistance and other variables of ventilation. C, V_T max V_{in} and V_E are given adjusted and non-adjusted for weight.

	C	V_T	max P_{in}	max P_{ex}	max V_{in}	max V_{ex}	freq	V_E	V_{TG}
R	−.228	059	464	297	251	182	24	227	148
Adj R	190	006			217			187	

Table 10. Correlations between thoracic gas volume and other variables of ventilation.

	C	R	V_T	max P_{in}	max P_{ex}	max V_{in}	max V_{ex}	freq	V_E
V_{TG}	148	210	.051	369	150	147	.089	048	.070

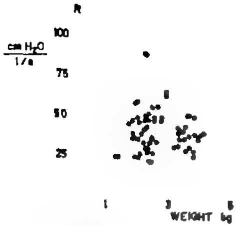

Fig. 3. Pulmonary resistance in healthy newborns in relation to body weight.

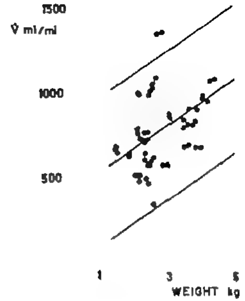

Fig. 4. Total ventilation in healthy newborns in relation to weight. Lines denote *mean and limits of 95 % confidence interval.*

with other variables of ventilation is shown in Table 9. In multiple regression

$$R = 77.0 - 4.4\,C - 0.073\,V_{in} - 0.299\,f \qquad (2)$$

with approximately normally distributed residuals. The coefficient for f was not significant and the reduction in the variance of R by regression on weight was only 16 % giving a standard error of 15 $cmH_2O/(l/s)$.

Thoracic gas volume, V_{TG} was measured in 31 infants on 50 occasions. Thoracic gas volume was best correlated to body length in the sample,

$$V_{TG} = 1.85\,l - 0.8 \qquad (3)$$

where l is body length in cm.

The coefficient of regression, however was not statistically different from O. Mean V_{TG} was 87 ml, S.D. 28 ml, range 44–145 ml. The correlations of V_{TG} with other variables of ventilation is shown in Table 10. Only $maxP_{ex}$ gives a significant correlation. V_{TG} did not differ significantly when measured during the first 12 hours of life and later (Table 6).

Other variables (Table 4). The *maximum inspiratory and expiratory flow, tidal volume and ventilation* (Fig. 4) were all body size dependent and highly intercorrelated. The *breathing frequency* did not show any body size dependence and was not related to gestational age although more irregular breathing patterns were seen in the pre term infants. The breathing frequency was negatively correlated to pulmonary compliance in the primary material but the relation was not significant in the regression equation presented above. Frequency was also correlated with negative sign to pulmonary resistance. The *pressure measurements* did not show any sure correlation to body size.

The reliability of the measurements of R and C is difficult to determine as the variation in the parameters from one measurement to another is influenced not only by the procedure of measurement but also by other variables of ventilation which are subjects to considerable variation. The breath to breath variation and the variation between two measurements performed on separate days within one week after the first 24 hours of life appear in Table 11.

Discussion

The healthy and the sick newborns were examined under identical conditions i.e. in an incubator at or near neutral temperature exposed to the almost naked body including the temperature sensitive

Table 11 Breath to breath and day to day variation in lung compliance and resistance in healthy newborn infants.

	Compliance	Compliance ml/cmH_2O	Resistance $cmH_2O/(l/\ )$
Breath to breath variation			
mean sample S D		0 61	10
number f observations per sample		16	16
Day-to-day variation			
mean difference	term	–0 42	3.8
	preterm	–0.10	8 0
S.D f difference	term	0.75	17
	preterm	1.25	24
number f observed individuals	term	10	10
	preterm	10	10

trigeminal area in the face For most control babies these conditions were different from those in routine care, and this may have influenced the measured variables. Because of this the results from the group of healthy newborns were suitable as reference values in comparisons with sick babies but will not necessarily be identical with results from healthy infants under usual nursing conditions.

A body size dependence was expected for variables of ventilation because of the relation of metabolic rate to body mass, and for mechanical parameters because of the relation of body size to lung size. These relationships were confirmed in this study except in the case of pulmonary resistance In adults this parameter and its component – airway resistance – are dependent on lung size and airflow (28) However pulmonary resistance in this study was not size dependent, and this finding in infants appears reasonable from a theoretical point of view as flow resistance in airways with small dimensions will be more affected than will larger ones by small absolute variations in diameter Moderate differences in the architecture and the status of the mucosa in parts of the airways may give rise to marked *difference in flow resistance*. This factor was probably responsible for the wide range of pulmonary resistance observed.

A correlation of lung compliance to body size is usually found if the sample is not too homogenous in size (13) To minimize the size dependent variation, compliance in different studies has been related to lung volume predicted lung weight length, length to the power of 3 or near 3 and weight. For comparison of compliance over a wide range of body size lung volume or body length is often the preferred reference standard (13) In neonates Karlberg et al (22) found a better correlation to length than to weight. However in the present study body weight showed a better correlation with compliance and was correlated to most other variables at the same level as was length and length to the power of 3 Therefore we have used body weight as a somatic reference standard for pulmonary measurements, except V_{TG} which was related body length.

In this study *mean dynamic lung compliance* at 3 kg body weight was 3.9 ml/cmH_2O This value is lower than that reported by Cook et al, (12) Karlberg et al, (22) Swyer et al (44) and Chu et al (9) who found mean values of 4 7 – 6.0 ml/cmH_2O in the same weight group but is in the same range as data published by Reynolds et al (38) and Griffin et al (18) who found C_1 to be 3.3 and 3 7 ml/cmH_2O respectively The differences may be a result of different methods of sampling of breaths and of different calculation technique. Differences in methods used for recording of flow and pressure may also play a role (see section II). The observed increase in pulmonary compliance during the first day of life is well documented (9 16 22) The

increase in compliance was not accompanied by a change in V_{TG} and was probably related to mechanical changes in the lung parenchyma (9)

The lack of correlation between pulmonary compliance and thoracic gas volume was unexpected and differs from other studies (8 9) It is well known that static lung compliance increases with increasing lung volume and that the ratio C/FRC is fairly constant at different ages during growth (13) In the same individual however the C/V_{TG} ratio is not constant but dimінis when volume increases (1 4) This is the probable reason for the low compliance demonstrated in some infants with very high lung volumes (Figure 2) The marked variability in lung volume in newborn infants probably due to air trapping, is well documented (8, 9 25 31) and is reflected in this study by the lack of significant correlation between body size and V_{TG} in the material. Consequently the type of C/V_{TG} relation demonstrated in Figure 2, is to be expected in a material where V_{TG} varies independent of body size

In adults it has been shown that lung compliance during breathing is frequency dependent if time constants in different part of the lung are not equal. In healthy adult lungs (33) and in healthy infants (47) frequency dependency of lung compliance or resistance is not demonstrated In this study before "partialling out" via multiple regression there was a significant negative correlation between lung compliance and frequency This correlation, however diminished and was insignificant in the multiple regression analysis. It is important to point out, that these calculations are purely descriptive and no conclusion about causality can be drawn from the presence or lack of correlation and regression A shown relation between two variables may be quite indirect and mediated by other variables. A negative correlation between lung compliance and frequency in a sample of observations may be a demonstration of inhomogenous mechanics in the lung, a result of an adjustment of the breathing pattern (V_T/f-relation) in response to different elastic recoil of the lungs, or the sum of both processes. In multiple regression analysis the coefficients may be influ-

Table 12 Newborn infants with pulmonary disease

		All diseased infants			HIGH R		
		mean	S.D	range	mean	S.D	range
R	$\frac{cmH_2O}{l/}$	61	25	20–198	110*	44	77–200
$C^{1)}$	$\frac{ml}{cmH_2O}$	1 4	1 1	– 09–3.2	0 85	0 76	62 2.4
$V_T{}^{1)}$	ml	8.2	2.9	2.4 16.0	7 4	2.5	2.4 11 1
mi. P_m	cmH_2O	8 2	3.3	3.2 17 6	9 6	1 4	7 7 12.2
max P_{ex}	cmH_2O	2.4	1 3	0.6 8 6	4 6	2.1	1 4 8.6
max $V_m{}^{1)}$	ml/	56	22	16 134	53	21	21 84
f	min^{-1}	81	23	45 136	68	15	45 95
$V_E{}^{1)}$	ml/min	710	340	200 1980	530	200	270 940
V_{TG}	ml	62	39	0 141	61	35	29 115
F_iO_2	%	42	16	21 90	48	22	21 90
$DurO_2{}^{2)}$	day	3 4	2 4	0 9 0	3.6	2 9	0 9.0
weight	g	2780	1000	870 5140	2660	1190	870–5140
length	cm	48	4.3	37–56	47	5 3	37 56
gest age	weeks	36	3 7	26–43	35	4.6	26 42
n 3)		36 (29)			10 (7)		

1) Adjusted to 2 kg body weight
2) Surviving infants only
3) n for V_{TG} in parenthoses

Asterics indicate significant deviation from the mean of the reference group for $0.05 > p \geq 0.1$ for $p < 0.01$

enced by potent variables not included in the equation, if such variables exist, and their coefficients of regression. If they were insignificant in the presented equation, (eq 1) as was suggested by the normally distributed residuals, the significant regression of C on f in the primary results dissolved when the regression of C on other variables are taken into consideration. If C is predicted from the presented equation of regression (eq. 1) variation in f is of minor and insignificant importance. There is a strong correlation between C and V_T (0.67) which is maintained in the multiple regression equation. This result most probably shows that a high lung compliance allows the muscles of breathing to perform high tidal volumes and *vice versa* suggesting that the dynamic lung compliance is a factor of importance in the regulation of tidal volume.

The mean pulmonary resistance, 42 $cmH_2O/(l/s)$, S.D 16 $cmH_2O/(l/s)$ was somewhat higher than most values previously reported. Cook et al (12) measured 29 $cmH_2O/(l/s)$ in mature newborns and mean values from Swyer et al (44) and Polgar et al (35) were 26 and 34 $cmH_2O/(l/s)$ respectively. Karlberg and Koch (22) noted mean values of about 30 $cmH_2O/(l/s)$ and Luft et al (26) 51 $cmH_2O/(l/s)$. The method used in present study with the esophageal catheter inserted through the right nostril most likely provided the higher resistance measures. This method was however preferred because of a lower degree of irritation and a diminshed tendency to vomiting as noted compared to the oral route.

The correlations between R and other variables in the samples were of somewhat less magnitude than the correlations of compliancee. R was correlated to both max. inspiratory and expiratory pressure. This may mean either that expiratory muscles were active or that end expiratory volume was elevated resulting in elevated elastic pressure available for expiration when R was high. As was the case with the frequency dependence of compliance, the significant, negative correlation between R and f was dissolved in the multiple regression equation and must be interpreted with caution.

NORMAL R			LOW C			NORMAL C		
mean	S.D	range	mean	S.D	range	mean	S.D	range
42	14	20 68	65	43	27 198	43	22	20 88
1 6	1.2	– 09–5.2	0.89	41	0 09 1 6	3 0	1.2	1 9 5 2
8.7	3.0	3.7 16 0	7 7	2 5	3 7 13 9	10 1	3 0	6.1–16 0
7 7	3 8	3.2–17.6	9 2	3 1	4.9 17 6	5 0	2 1	3.2 9 9
1 6	86	0.6–3 4	2 5	1 9	0 7 8 6	1 8	1.2	.6 3 4
58	23	16 134	59	26	16–134	54	18.1	18 77
85	24	[illegible] 136	86	25	45 136	71	20	48 108
780	370	200 1980	74.0	580	190 1980	740	280	340–1160
62	41	10–141	59	40	0 141	71	4 0	10–141
39	13	21–60	45	17	21 90	31	7 9	21 50
3.4	2.2	0–8.0	3.8	2.4	0–9.0	2 4	2.0	0 70
2840	940	1520–4480	2600	1010	870–5140	3310	830	1700 4480
48	3 9	43–54	47	4.3	37 56	51	2.7	46 54
37	3 5	30–43	36	3 9	26–43	38	3.2	34–41
26 (22)			27 (20)			9 (9)		

The thoracic gas volume of the healthy infants was within the range previously reported (2 9 23 31 36) Although marked changes in V_{TG} *during the* first days of life were seen in some individuals there was no significant such trend in the material as reported by Burnard et al (8) and Thibeault et al (45) The number of studies per infant was however small.

The breathing frequency was higher than reported for newborns during basal conditions (11 14) This was probably mainly due to the temperature in the incubator but the disturbing influence of the nasal catheter or to the brevity of the adaptation period in the apparatus may have *played a role*

Tidal volume was somewhat lower than most other reported on infants in basal conditions but in the *same range as reported by Prod'hom et al (36) and* Nelson et al (30) A reduced tidal volume may be expected, according to Prod'hom et al (36) as a result of the high frequency of breathing. The *ventilation* was calculated from usually 16 breaths. Such a sample does not cover a long time interval but is representative for the period of sleep chosen. The ventilation is much higher than the "basal" values of Cross (14) higher than those of Cook et al (11) and Prod'hom et al (36) but in the same range as the results of Deming and Hanner (15) and Harrison et al (20) These differences between findings in ventilation are accompanied by differences in breathing frequency

Results. II. Infants with pulmonary disease

In the total group of diseased infants the mean lung compliance was decreased and mean lung resistance was increased (Table 12). Clinically however the group was not uniform because it included infants with diseases of varying severity and different lung X-ray appearance With respect to intervals of confidence of the reference group the sick infants could be separated in one group with lung compliance within normal range ("normal C" n = 9) and another with lung compliance below the 95 % confidence interval ("low C" n = 27). In similar way the material was also divided in one group with lung resistance above the 95 % confidence interval ("high R" n = 10) and another with normal lung resistance ("normal R" n = 26) The infants are presented in the Appendix and group means for variables measured are compared and related to reference values in Table 12. As *reference values* for ventilatory variables means of the *reference group* are used, adjusted for body weights using the equations in Table 4 but not for the influence of *other correlated* variables.

The infants in the low compliance group had a higher lung resistance than the reference group a reduced tidal volume wider pressure swings and a reduced V_{TG}

The sick infants with normal compliance differed from the reference group in tidal volume only

The two groups differed from each other significantly in maximal inspiratory pressure. Maximal *inspiratory oxygen concentration used for therapy* differed also (Table 13)

Table 13 Differences between groups of diseased infants differing in resistance and compliance

	Low C – normal C	*High R – normal R*
R	22	68
$C^{1)}$	−2.1	0 7
$V_T^{1)}$	2.4	1 3
max P_{in}	4.2	1 9
max P_{ex}	0 7	3 0
max $V_{in}^{1)}$	5	5
f	15	17
$V_E^{1)}$	0	250
V_{TG}	12	1
FO_2	14	9
DurO_2	1 4	0.2

1) Adjusted to 2 kg body weight.
indicates significant difference ($p <$ 0 05)
Units as in table 12.

The group selected for high lung resistance showed reduced pulmonary compliance and tidal volumes, increased pleural pressure swings, reduced ventilation and V_{TG} *in relation to the reference group.*

The normal resistance group differed from the

reference group by low lung compliance and tidal volumes, high inspiratory pleural pressure and a reduced V_{TG}. The groups with high and normal resistance differed from each other except in lung resistance in max. expiratory pressure ventilation and frequency the high resistance group having the lower frequency

After recovery complicance and V_{TG} was still reduced in the "high R group and breathing frequency was reduced in the "low C" group. Others parameters were normalized. (Table 15).

Mechanical parameters related to diagnosis

According to criteria given below the infants were given different clinical diagnoses.

a) Idiopathic respiratory distress syndome (IRDS)

1) Signs of respiratory difficulties with increased frequency (>60 breaths per minute).

2) Hypoxia when breathing room air

3) Diffuse reticulogranular pattern and air bronchogram on chest roentgenogram.

b) Suspect IRDS

1) and 2) as above

3) Not diffuse or not entirely typical reticulogranular pattern.

c) Aspiration syndrome

1) as above

2) Coarse and irregular pattern on chest roentgenogram often combined with pleural liquid

d) Unclassified disorders

1) as above

2) Focal or diffuse pathological pattern not assignable to patterns under a to c and with or without pneumothorax or pneumomediastinum.

Twelve infants fullfilled criteria for IRDS, while in six infants with minor deviations from the x-ray criteria this diagnosis was suspected. Eleven infants had aspiration syndrome and in seven newborns the clinical findings were not compatible with any specified diagnosis. They were referred to as unclassified lung disease Three of these infants had a pneumomediastinum or a small pneumothorax together with infiltrates in the lung parenchyma.

Group results appear in Table 14 The individual infants within the groups are presented in the Appendix.

The differentiation of the IRDS-infants into two groups depended on X-ray findings only The clinical behaviour was similar However among all variables measured, only breathing frequency and max. inspired oxygen concentration differed. This will be discussed later For further description and discussion the groups of definite IRDS and suspect IRDS are brought together and called IRDS.

IRDS.

The combined IRDS-group comprised 18 infants with mean birth weight of 2070 g (range 870–3360) and mean gestational age of 34 weeks. The mean of maximum oxygen concentration given to the infants in this group to maintain the Pa_{O_2} at 50–80 mmHg was 52 % (30–90 %) and mean right to-left shunt calculated measured after the plethysmographic study was 30 % range 17–48 %. The mean duration of the oxygen therapy was 5.3 days (2.3–9 days).

Lung compliance was reduced and below the one-tailed 95 % confidence interval of the reference group for every infant in the IRDS group (Figure 5). The exact relationship between the development of C and the course of the disease cannot be calculated from this study as it was not possible to study the infants at intervals short enough during the disease However C in some cases decreased from the first to the second (or following) measurement, and generally the lowest C was recorded when the calculated shunt was highest. Before correction for body weight C during the disease was weakly correlated to R ($r = -469$( ) 16 d.f., $p = 0.05$)

After correction for body weight there was no significant correlation between adjusted C and R and the strong correlation to V_T found in the reference group was not seen.

After recovery C was normalized (Table 15).

Lung resistance As demonstrated in Table 14 mean lung resistance in the IRDS group was

Table 14 Observations after recovery

		DEFINITE IRDS			SUSP IRDS			A IRDS (total group)		
		mean	S.D	range	mean	S.D	range	mean	S.D.	range
R	$\frac{cmH_2O}{l/s}$	68	43	32–175	70	65	27–200	69	49	27 200
C 1)	$\frac{ml}{cmH_2O}$	.91	.26	.54–1 4	.62	.52	.09–1 3	.81**	.38	–.09–1 4
V_T 1)	ml	7 1	2 0	3.7–10 4	6 4	.99	5 2–7 8	6.9	1.6	3.7–10 4
$\max P_{in}$	cmH_2O	9.2	3.1	4 9–16.5	10 9	4.6	6 2–17 6	9.8**	3 6	4 9–17.6
$\max P_{ex}$	cmH_2O	2.2	2.4	7–8.6	2.1	1 4	9–4 6	2.2	2.1	7 8.6
$\max \dot{V}_{in}$ 1)	ml/s	47	20	16–84	59	19	39–92	49	20	16 92
f	min^{-1}	74	19	45–105	101	28	71–136	83	25	45–136
$\dot{V}_E$ 1)	ml/min	560	240	200–1030	720	330	390–1240	610	280	200 1240
V_{TG}	ml	44	29	0–102	25	25	0–48	40	28	0 102
F_IO_2	%	58	15	30–90	41	12	30 60	52	16	30 90
dur_{O2} 2)	days	5 4	2.3	2.3 9.0	4.5	1.3	2.3 6.0	5.3	2.0	2.3–9 0
weight	g	1950	550	870–2730	2310	660	1520–3360	2070	600	870 3360
length	cm	44	3.1	37–48	45	24	43–49	44	2.9	37–49
gest. age	weeks	33	3.2	26–36	35	2.1	32–38	34	2.9	26–38
			12			6			18	
n for V_{TG}			10			3			13	

1) Adjusted to 2 kg body weight
2) Surviving infants only
Asterisks indicate significant difference from the mean of the reference group $0.05 > p \geq 0.01$ $p < 0.01$

Table 15 Observations in diseased infants.

	IRDS			ASPIR.			LOW C		
	Mean	S.D	Range	Mean	S.D	Range	Mean	S.D	Range
R	54	21 4	30–113	49	26.5	28–116	53	19	30 113
C 1)	3.2	0.61	2 3–4 7	3.8	0.94	2.5 5.2	3 4	0 69	2.3–4 9
V_{TG}	89	42	37–154	68	42	39–131	77	41	37 154
V_T 1)	14 7	3.6	10.0–24 0	12 7	2.3	9 6–16.1	14 7	36	9 6 24.0
f	46	7.8	29 57	65	18	41–88	49	9.2	29 67
vem 1)	690	240	300 1270	770	220	470 1070	720	230	300 1270
n		16			8			20	
$^nV_{TG}$		12			4			14	

1) Means adjusted to 2 kg body weight
Units in Table 12
Asterisks indicate significant difference from the mean of the reference group $0.05 > p \geq 0.01$ $p < 0.01$

B ASPIRATION SYNDROME mean	S D	range	C UNCLASS. DISORDERS mean	S.D	range	Significant differences between groups
48	20	20–79	54	35	21–115	
1.3	64	16–2.3	3 2	1 4	1 3–5.2	A < B C
8 8**	2.8	5.3 13 9	11.5	2.3	9 6–16.0	A < B C
6.9	2.1	3 6–9.2	6.1	2.7	3.2 9 9	A > B C
2.3	1 7	.6–5.8	2 6	1 0	1.0–3.4	
[illegible]	31	18–131	56	15	30–76	
[illegible]	27	48 135	67	11	55 83	A > C
930	450	340–1980	790	240	520 1080	A < B
72	42	[illegible] 140	99	37	36–141	A < C
29	3 4	21 34	34	9.8	21 50	A > B C
2.1	1.8	0 7.0	1 9	1.8	0–4 0	A > B C
3490	860	1700 5140	3500	700	2600–4480	A < B, C
51	2.5	46–56	51	3 0	46–54	A < B C
39	3.1	32–43	39	2.9	34–41	A < B C
	11			7		
	8			6		

NORM C Mean	S D	Range	HIGH R Mean	S.D	Range	NORM R Mean	S.D	Range
54	42	28 116	46	11	39 116	54	25	28–113
4 3	0 95	3.1 5 2	2 8	0 42	2.4 3 0	3 6	0 85	2.3–5.2
93	54	54 131	54	10 1	38 62	91	42	37 154
12 6	2 0	10.7 15 3	14 4	3.4	9 6–19.5	14.3	3 6	10 0 24 0
[illegible]	21	41 [illegible]	52	8 2	37 59	50	13	29 88
720	240	460 1010	750	220	550–1070	710	240	300 1270
	4			5			[illegible]	
	2			3			13	

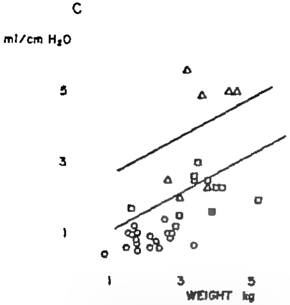

Fig. 5 Pulmonary compliance in diseased newborns. ○ denotes IRDS, □ aspiration syndrome, and △ unclassified lung disorders. Mean and limit of one-tailed 95 % confidence interval for healthy infants are marked

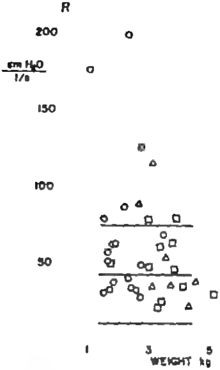

Fig. 6 Pulmonary resistance in diseased newborns. Lines denote mean and 95 % confidence interval. Symbols as in Fig. 5

creased but the individual values had a very large range (27–200 $cmH_2O/(l/s)$ (Fig. 6). In several infants the high R was clearly related to grunting. Grunting, however, appeared in different degrees and there was no distinct differentiation between grunting and "not grunting" breathing. Because of this it was not possible to determine exactly how many registrations were recorded during grunting. On the other hand in some registrations with evident grunting the lung resistance was not high. This can be explained by the mode of onset and the duration of the closure of the vocal cords during grunting. In infants who demonstrated grunting as well as non-grunting breathing during a recording the non-grunting breaths were used for calculations.

R in this group was significantly correlated to C (–.469*) max P_{tn} (.617 *) and frequency (–.508*)

In those infants who had a high initial lung resistance the lung resistance normalized more rapidly than lung compliance did. After recovery defined above mean resistance was not significant ly increased but breathing frequency was reduced.

Thoracic gas volume. Values of thoracic gas volume during the acute phase usually came from the examination at the peak of the disease. If data were missing on this occation and values from examinations earlier during the disease were available the value most close in time to the peak of the disease was used. Mean V_{TG} in this group was 40 ml, S.D. 28 ml, range 0–102 ml, which was significantly lower than the reference group. Low V_{TG} was in most cases associated with low lung compliance as could be expected from a mechanical point of view (Fig. 7). V_{TG} seemed to normalize together with lung compliance and clinical appearance but variations were common. After recovery V_{TG} was restored to the level of the reference group.

Tidal volume. Mean tidal volume was 7.0 ml ($V_{T(2kg)}$[1]) = 6.9 ml) (range 3.0–11.3 ml), significantly lower than the reference group.

V_T normalized together with frequency of breathing.

[1]) Variables with significant weight dependency in the reference group are also given adjusted to the body weight of 2 kg. This adjustment is based on the regression found in the reference group.

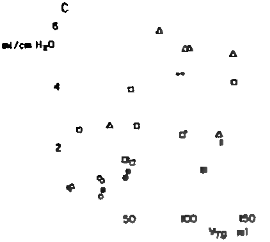

Fig. 7 Pulmonary compliance in healthy and diseased newborns in relation to thoracic gas volume. Symbols as in Fig. 5

Pressures. Mean maximal inspiratory pressure was 9.8 cmH_2O (range 4.9–17.6 cmH_2O) and significantly higher than the reference group.

There was no significant increase in maximal expiratory pressure.

Flow. Mean of the maximal inspiratory flow was 50 ml/s (range 14–101 ml/s) ($V_{in(2kg)}$ = 49 ml/s) and not different from the reference group.

The expiratory flow pattern was much affected by grunting as was demonstrated in flow-pressure diagrams, page

Breathing frequency. The breathing frequency was – as a criterium of selection – significantly increased. Mean frequency was 83/min, range 45–136. Infants with entirely typical lung X-ray (number 1–12 in Appendix) had lower frequency than those with some variation from the typical findings.

Ventilation. The mean ventilation was 620 ml/min, range 130–1440 ml/min, ($V_{E(2kg)}$ = 610 ml/min). The mean did not differ from the mean ventilation of the reference group after correction for body weight.

Some infants in the IRDS group, however having a typical X-ray, had very low ventilation (Fig. 8). As demonstrated in Figure 9 there was a negative correlation between Pa_{CO_2} and total ventilation, adjusted for body weight, in the acute phase with prominant hypoventilation among the infants with low total ventilation levels.

Aspiration syndrome

This group was made up of 11 infants with mean birth weight 3490 g with a range of 1700–5140 g. Mean gestational age was 39 weeks. The maximal oxygen concentration given to maintain Pa_{O_2} between 50 and 80 mmHg or to remove cyanosis was between 21 (i.e. no extra oxygen) and 34 %, with a mean of 29 %. The maximal oxygen concentration was negatively correlated to body weight. The mean duration of oxygen theraphy was 2.1 days (0.0–7.0 days)

Lung compliance. The mean lung compliance was 2.2 ml/cmH_2O, range 1.2–3.1 ml/cmH_2O. The mean adjusted to 2 kg body weight was 1.3 ml/cmH_2O. This was significantly lower than the reference group and the variance was also significantly reduced. In contrast to the IRDS-group not

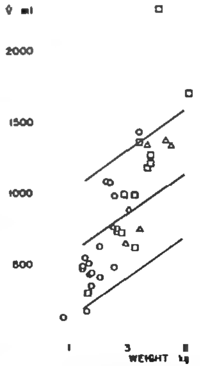

Fig. 8 Total ventilation in relation to body weight in diseased newborns. Lines denote mean and 95 % confidence interval of healthy infants. Symbols as in Fig. 5

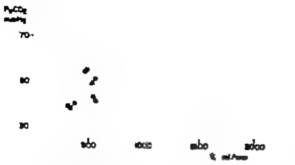

Fig. 9 Pa_{CO_2} in diseased newborns in relation to total ventilation, adjusted to 2 kg body weight. Symbols as in Fig. 5

every member of the group demonstrated lung compliance below the 95 % confidence interval (Fig. 5).

The finding of a reduced lung compliance in this group was always an isolated phenomenon that did not appear more than once in a series of studies in a patient. In all cases except two, the first registration was the pathological one.

Lung compliance in this group was positively correlated to max. oxygen concentration inspired ($r = 0.64$ 9d.f., $p < .05$)

Lung resistance. (Fig. 6) Mean lung resistance was 48 $cmH_2O/(l/s)$ range 26–79 $cmH_2O/(l/s)$. The mean did not differ from the reference group. Lung resistance in this group was correlated to maximal expiratory pressure ($r = 0.76$ 9df $p < .01$). Such a correlation may indicate that expiratory flow was maintained despite increased resistance as a result of contractions of the expiratory muscles or an increased end-expiratory volume leading to increased elastic recoil.

Thoracic gas volume. V_{TG} was measured in 8 infants. Mean V_{TG} was 72 ml with a very wide range 10–141 ml. The mean was not statistically different from the mean of the reference group

Other variables (Table 14) Mean tidal volume was reduced. Mean max. inspiratory pressure was increased but mean max. expiratory pressure did not differ from the reference group. Mean max. inspiratory flow was unaffected. Mean breathing frequency was increased. Mean ventilation was not significantly increased.

After recovery all variables measured accorded with the reference group

Unclassified lung disorders.

This group is presented in Table 14. The mean weight was *3530 g (2600–4480 g)* with a mean gestational age of 39 weeks.

Maximal oxygen concentration used varied between 21 (i.e. no extra oxygen) and 50 %, mean 34 %. The duration of the oxygen therapy was from 0 to 4 days, mean 1.8 days.

Lung compliance varied between 2.1 and 5.8 ml/cmH_2O. The group mean was 4.0 ml/cmH_2O ($C_{(2kg)} = 3.2$ ml/cmH_2O) did not differ from the reference group but two individuals had compliance values below the 95 % confidence interval. The standard deviation was large (Fig. 5)

Lung resistance varied between 21 and 115 $cmH_2O/(l/s)$. The group mean, 54 $cmH_2O/(l/s)$ did not differ from the reference group. The standard deviation was large (Fig. 6)

Thoracic gas volume was measured in 6 patients and was 36 to 141 ml. The mean 99 ml was not significantly different from the reference group. The standard deviation was large

Other variables (Table 14) Tidal volumes max. inspiratory pressure, max. inspiratory flow breathing frequency and ventilation did not differ significantly from the reference group. The only difference was found in mean expiratory pressure which was bigger than the corresponding mean in the reference group

Pressure-volume diagrams

Pressure-volume loops had an essentially homogenous appearance in the healthy newborn. As shown in Fig. 10 the inspiratory and expiratory part form a loop with the appearance of a biconvex lens. Usually there was a very small or no bulge of the loop to the left of the X-axis but sometimes a larger bulge was seen.

In infants with pulmonary disease different types of deviations were present. Bent loops

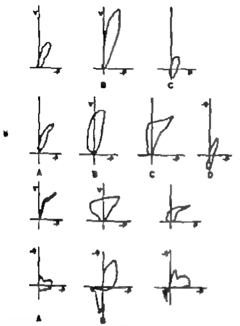

Fig. 10. Volume-pressure and flow-pressure diagrams in healthy and diseased infants. Original registration.
I. Healthy newborns
II. Aspiration syndrome. A, B, and D during ordinary breathing, C during grunting.
III. IRDS. A. Bent loop pattern. B and C: Different degrees of grunting. Note the concave inspiratory part in figure C, upper diagram.

were sometimes seen, mainly in IRDS. Grunting infants showed a pattern with a triangular loop (Figure 10). This pattern was not reserved for IRDS only but was sometimes seen in cases of aspiration syndrome and other diseases. The inspiratory part was straight, concave, S-shaped or convex. The flow record was typical and gave a peculiar pressure-flow-diagram with a rosette-like formation (Figure 10). In grunting infants periods of hard grunting often were interrupted by non-grunting breathing. Intermediate forms were common with a slightly or markedly elongated expiration and a loop pattern as in Figure 10, III C.

In non-grunting infants with aspiration syndrome or with unclassified conditions the volume-pressure diagram often looked normal but a bulge of the loop to the left side of the volume-axis was common, indicating high expiratory resistance or/and high expiratory flow.

As described in the preceding section an attempt was made to quantify the signs of non-linearity in the mechanical parameters seen in the diagrams by calculating separate compliance values during the first, C_1 and second, C_2 half of the inspiration. The ratio C_1/C_2 was calculated in 34 healthy newborns, in 9 infants with IRDS, in 8 infants with aspiration syndrome and in 4 infants with unclassified lung disorders. The result is presented in Table 16.

Table 16 C_1/C_2 in healthy and diseased subjects.

C_1/C_2	Healthy infants	IRDS	Aspiration syndrome	Unclassified disorders
mean	0.81	1.37	1.07	0.75
S.D	0.20	0.44	0.36	0.20
	34	9	8	4

indicates significant difference, $p<0.01$ from the mean of the healthy group. Differences in C_1/C_2 between groups of diseased infants were not significant ($p>0.05$).

Summary of results and relationships between the variable means of the three groups of diagnoses

The IRDS group had lower *birth weights* and gestational ages than any other group. They required higher *oxygen concentration in inspired air* especially those with a entirely typical X-ray picture, than the other groups and the *duration of oxygen therapy* was longer.

Lung compliance was lower than in both the other different from other patient groups,

lung resistance was increased but not significantly different from other patient groups,

thoracic gas volume was decreased and lower than the unclassified patients but not significantly different from the aspiration syndrome

tidal volume was decreased and lower than other patient groups,

max. inspiratory pressure was higher in the IRDS-groups but *max. expiratory pressure* was not increased,

max. inspiratory flow was not increased as in the other groups,

breathing frequency was increased by definition and higher than the unclassified group,

ventilation was not increased and lower than in aspiration syndrome

The aspiration syndrome group had *higher weight* than IRDS required less *inspiratory oxygen concentrations* and *the duration of oxygen treatment* was shorter In these respects this group did not differ from the unclassified infants.

Lung compliance was transiently reduced but the mean was higher than in IRDS

Lung resistance and *thoracic gas volume* differed from neither the IRDS-group nor the reference group

Tidal volume was reduced but less than in the IRDS-group.

Max.inspir pressure was increased but less than in the IRDS-group

Max.expir pressure and *max.inspiratory flow* were unaffected.

Breathing frequency was increased by definition and not different from IRDS.

Ventilation was higher than IRDS but not significantly higher than the reference group

The unclassified group. The mean weight, max. in d oxygen concentration and duration of oxy therapy did not differ from the aspiration syndrome

Lung compliance, resistance thoracic gas volume tidal volume, max. inspir pressure, flow breathing frequency and ventilation did not differ from the reference group but the *max. expiration pressure* was increased.

Discussion

In a radiological study Peterson and Pendleton (34) demonstrated that newborn infants with respiratory distress could be separated into two main groups, one with reticulogranular pattern on lung X-ray and another with a course and irregular pattern. Very few infants could not be classified in this way The first group showed high mortality and was strongly correlated to the finding of hyaline membranes in the lungs at autopsy when in the other group only few infants died, and the lungs were focally crepitant and showed microscopically focal atelectasis and emphysema, together with large amounts of keratinized squamous cells in the airways sometimes together with meconium. The second group was referred to as "fetal aspiration syndrome"

Prod'hom et al (37) in a physiological study were able to separate distressed newborns in three groups based on the degree of rigth-to-left shunt. Group I comprised infants with abnormally high and increasing shunt during the first day and reticulogranular pattern on lung roentgenograms. Group II had normal right-to-left shunt, sometimes slightly increased during the first day of life The lungs showed peribronchial infiltrations often associated with hyperinflation in all cases except one who showed a reticulogranular pattern. A small group III had transient initially abnormal right to-left shunt and roentgenograms suggesting aspiration.

These results including the demonstration of low lung compliance have been confirmed by Chu et al (10) in infants corresponding to group I and by Sundell et al (43) on infants corresponding to group II Consequently the two main groups described by Peterson and Pendleton have been demonstrated to differ also in pathophysiology and in prognosis. Clinically they are associated with 'idiopathic respiratory distress syndrome (39) or 'hyaline membrane disease and aspiration syndrome or 'type II respiratory distress syndrome (37 43) respectively

In this study a *low dynamic lung compliance* was not confined to infants with IRDS (Table 17). By lung compliance measurement in newborns with lung disorders it was possible to select one group of infants more severely affected than another This severely affected group of infants with low compliance included the complete IRDS group. The nine other infants, however, were not similar to the IRDS group in V_{TG}, oxygen requirements, duration of disease or other signs of severity of disease (Appendix) and were less affected. This means that together with the IRDS group there existed another group of infants with reduced compliance without a severe clinical disease. Because of this the criteria for IRDS-diagnosis (page 37) will select a more severely affected group than an isolated finding of low lung compliance This is a demonstration of the specifity of the pattern of the roentgenogram in IRDS, and the reticulogranular pattern on chest roentgenograms seems to be firmly related to disturbed lung mechanics at the peak of the disease On the other

Table 17 Relations between C-group R-group and diagnosis in the diseased infants. Digits represent numbers of infants in each group.

	LOW C: IRDS susp.	LOW C: IRDS definit	LOW C: IRDS	LOW C: ASPIR.S.	LOW C: UNCLASS.	LOW C: total	NORMAL C: IRDS	NORMAL C: ASPIR.S.	NORMAL C: UNCLASS.	NORMAL C: total
HIGH R	1	4	5	3	1	9	0	0	1	1
NORMAL R	5	8	13	4	1	18	1	4	4	8

hand the results show that there seems to exist a group of newborn infants with increased breathing frequency and pathologic, radiologically visible lung parenchyma changes without any reduction in lung compliance. This group also had a normal resistance and no distrubances in ventilation and ventilation pattern except for a reduced tidal volume. In contrast, the infants with reduced lung compliance also, on the average, had a high lung resistance and abnormal pleural pressures and flows and V_{TG} was low. Despite a reduced tidal volume the ventilation was within normal limits.

The infants in the group with reduced lung compliance were more affected than in the other. They needed higher concentrations of oxygen (45 % against 31 % in the group with normal compliance) and the duration of oxygen therapy seemed to be longer although the difference is not significant. The infants who died belonged to this group. They were also shorter and the gestational ages were lower than in the other group.

The two groups formed by differences in lung resistance were more similar to each other in othe respects measured (Table 13). *High resistance* was seen to be combined with a reduction in frequency of breathing, a (not significantly) lower maximal inspiratory flow rate and a reduced ventilation, all in comparison with the infants with lung resistance within normal limits. Lung compliance seemed to be a more critical parameter than lung resistance to differentiate infants with respiratory distress with radiological evidence of lung disease with respect to degree of severity of the disease.

Normal lung compliance in diseased infants was associated with normal ventilatory parameters. The corresponding thesis does not hold for *lung resistance* calculated as an average over the whole breath. The topography of the resistance is unknown and it is not possible to separate contributions from different parts of the lung and airways with the method used. This is an important limitation of the clinical usefulness of the resistance parameter. The high R associated with low C is often due to grunting and the pressure flow pattern does not in any case indicate a high inspiratory resistance in IRDS. Calculations of inspiratory resistance easily performed by the calculating method used, are not conclusive however in cases with apparent nonlinear mechanical parameters as often is the case in IRDS. Consequently high R values calculated as averages over the whole breath may derive its origin from pathological processes in the lungs, in the lower or upper airways including activity in the glottis or the vocal cords. It is understandable that resistance has less discriminative power than compliance in separating infants more or less affected by lung disease.

The low lung compliance in the *IRDS group* confirms results from earlier studies (10, 37). The decrease in lung compliance during the first p
of disease found in some infants, may re

progress of the lung disease It may also be a result of oxygen therapy which may have this effect in healthy infants (31). *The low thoracic gas volumes* found in the IRDS-group are in agreement with earlier studies, (2, 6)

In agreement with Prod'hom s studies (37) the *aspiration syndrome* showed a reduced lung compliance with a mean between that of IRDS and that of the reference group. In this study the reduced compliance however was transient compared to the IRDS cases and seems not to imply any disadvantage for the lung function as lung *compliance in this group adjusted for weight* differences, was positively correlated to maximal oxygen concentration used in the breathing gas. The mean V_{TG} was reduced which is in variance with the results of Prod'hom et al but the variation was very large.

Though the tendency to a low lung compliance is strong the aspiration syndrome does not show such a uniformity in variables examined as IRDS. This may be a result of the different degrees of lung involvement seen in lung radiographs.

The most striking *clinical* differences between the aspiration syndrome and IRDS is, seen retrospectively the higher birth weights, the much smaller requirements of oxygen assigned by Prod'hom et al (37) and Sundell et al (43) to less right to-left shunting, the dissimilar roentgenograms *and a shorter and more favorable course* in aspiration syndrome A maintained reduction of lung compliance however suggests IRDS.

The group of distressed *infants without classified changes* on chest roentgenograms was – as expected – not uniform *regarding* mechanical and ventilatory parameters. The means did not differ from the reference group with one exception (max P_{ex}) but also this group includes two infants (number 35 and 36 in Appendix) with reduced compliance

IRDS as well as aspiration syndrome was associated with a low tidal volume, regardless of values on mechanical parameters Mean ventilation was however within normal limit, except in the smallest infants with IRDS who were low In this group hypoventilation is demonstrated (Figure 9) The failure to maintain adequate alveolar ventilation in the smallest and most immature infants in this study is discussed in the following section. The results on tidal volume and ventilation in IRDS are in agreement with studies by Miller et al (29) and Chu et al (10) but at *variance with results* reported by Cook et al (1?) Karlberg et al (21) and Prod'hom et al (37) who found normal or increased values The reason for this difference is not clear

The reduced tidal volume together with the increased frequency of breathing at maintained level of ventilation is in agreement with the theory of the adaptation of the ventilatory pattern to the least ventilatory work (32), adapted to healthy newborn by Cook et al (12) or with the theory of *Mead on adaptation to least average muscular force* (27). Presented results, seen from this point of view would imply that increased breathing frequency in a newborn infant with pulmonary disease may be a compensation for changed ventilatory mechanics and is not equivalent to an increased total ventilation.

Recovery here defined by the first registration made after clinical status was normalized and after the infant had begun to gain in weight, in IRDS was combined with a restitution of ventilatory and mechanical parameters with the exception of breathing frequency which was lower than in the reference group. This result differs from that of Bryan et al (7) who have shown a decreased lung compliance in a group of recovering infants with neonatal respiratory distress still at the age of one month. Such a tendency was seen in only one of our infants (number 2 in the Appendix). The reason for this difference in results is not clear

In several infants with IRDS non-linearity of the parameters of lung mechanics was suggested from the volume pressure loop pattern. As far as the volume-pressure loop is moderately bent, as demonstrated in the preceding section the non-linearity may be present in C K or both. In several cases of IRDS however the narrow loop is so much bent that the possibility of a linear C is not consistent with a positive sign of inspiratory resistance In these cases at least it must be presupposed that C is non-linear and C might alone be responsible for the bent loop pattern

In IRDS an increased elastic recoil has been supposed in studies in excised lungs (5) and a pathophysiological mechanism is suggested in the works concerning lack of surfactant agent in these infants (3 17). An increased elastic recoil is expected from the widespread athelectasis to-

gether with increased amounts of interstitial and airway liquid present in IRDS. At the same time a lack of surfactant will increase the elastic resistance to inspiration into alveoli still open. The bent loops seen in IRDS may illustrate these dynamics. The first part of the inspiration curve probably illustrates inhalation mainly against surface forces in open alveoli. The second part may reflect inhalation mainly against tissue forces after open alveoli having been critically filled. This kind of loop pattern may include more information on changed lung elastic behaviour than a reduced dynamic lung compliance. The C_1/C_2-ratio, introduced as a measure of non-linearity was remarkably efficient in separating infants with IRDS and aspiration syndrome from healthy individuals and infants with other lung disorders. Thus IRDS is characterized not only by a reduced lung compliance but by non-linear behaviour of C, R or both.

Uneven ventilation in IRDS has been shown to occur in lambs (46) and in infants (24) in studies with isotope techniques and frequency dependency of the parameters might hence also be expected, especially as the breathing frequency is high in IRDS.

The mechanisms responsible for the low compliance seen in aspiration syndrome and in some of the infants with unclassified lung disorders are less clear. Lung infiltrates may increase the elastic recoil by reducing lung volume or by interfereing with lung tissue elasticity. Unsimilarities in the mechanic impedance to flow in different parts of the lungs may also be responsible for a low compliance in these infants.

To what extent a low dynamic compliance found in a certain infant is a manifestation of an increased elastic recoil can not be determined from dynamic measurements. Measurements of static lung compliance in vivo in infants with lung disorders seem not to have been reported. When static measurements may give information on elastic recoil, dynamic measurements can be used to assess the functional state of the lung.

This study has shown that a low compliance in a newborn infant with respiratory disturbancies, determined after some hours of postnatal life implies an increased risk that a severe disease is present or develops. A solitary demonstration of low lung compliance per se is not alone conclusive but if repeated determinations show a remaining low or even lowered compliance, this indicates IRDS.

References

1. Agostoni, E., Volume-pressure relationships of the thorax and lung in the newborn. *J Appl Physiol*, 14:909, 1959.
2. Auld, P.A.M., Nelson, N.M., Cherry, R.B., Rudolph, A. J. & Smith, C.A., Measurement of thoracic gas volume in the newborn infant. *J Clin Invest*, 42:476, 1963.
3. Avery, M.E. & Mead, J., Surface properties in relation to atelectasis and hyaline membrane disease. *Am J Dis Child*, 97:517, 1959.
4. Avery, M.E. & Cook, C.D., Volume-pressure relationships of lungs and thorax in fetal, newborn, and adult goats. *J Appl Physiol*, 16:1034, 1961.
5. Avery, M.E., *The lung and its disorders in the newborn infant*. W.B. Saunders, Philadelphia, London, Toronto 1968, 2nd ed., p. 160.
6. Berglund, G. & Karlberg, P., Determination of the functional residual capacity in newborn infants. Preliminary report. *Acta Paediat Scand*, 45:541, 1956.
7. Bryan, M.H., Hardie, M.J., Reilly, B.J. & Swyer, P.R., Pulmonary function studies during the first year of life in infants recovering from the respiratory distress syndrome. *Pediatrics* 52:169, 1973.
8. Burnard, E.D., Grattan-Smith, P., Picton-Warlow, C.G. & Grauaug, A., Pulmonary insufficiency in prematurity. *Aust Paediat J*, 1:12, 1965.
9. Chu, J.S., Dawson, P., Klaus, M. & Sweet, A., Lung compliance and lung volume measured concurrently in normal full-term and premature infants. *Pediatrics*, 34:525, 1964.
10. Chu, J., Clements, J.A., Cotton, E.K., Klaus, M.H., Sweet, A.Y. & Tooley, W.H., Neonatal pulmonary ischemia. Part I. Clinical and physiological studies. *Pediatrics*, 40:709, 1967.
11. Cook, C.D., Cherry, R.B., O'Brien, [illegible], Karlberg, P. & Smith, C.A., Studies of respiratory physiology in the newborn infant. I. Observations on normal premature and full-term infants. *J Clin Invest*, 34:975, 1955.
12. Cook, C.D., Sutherland, J.M., Segal, S., Cherry, R.B., Mead, J., McIlroy, M.B. & Smith, C.A., Studies of respiratory physiology in the newborn infant. III. Measurements of mechanics of respiration. *J Clin Invest*, 36:440, 1957.
13. Cook, C.D., Helliesen, P.J. and Agathon, S., Relation between mechanics of respiration, lung size and body size from birth to young adulthood. *J Appl Physiol*, 13:349, 1958.
14. Cross, K.W., The respiratory rate and ventilation in the newborn baby. *J Physiol*, 109:459

15 Deming, J & Hanner J.P., Respiration in infancy II A study of rate, volume and character of respiration in healthy infants during the neonatal period. *Amer J Dis Child*, 51:823 1936

16. Drorbaugh J.E., Segal S Sutherland, J.M Oppé, T.E., Cherry R.B & Smith C.A. Compliance f lung during first week of life *Amer J Dis Child* 105:63 1963

17 Gluck, L. & Kulovich, M V Fetal lung development. Current concepts. *Pediat Clin N Amer* 20:367 1973.

18 Griffin, A.J Ferrara, J.D Lax, J.O & Cassels, D.E. Pulmonary compliance *Amer J Dis Child* 123:89 1972

19 Gupta, J.M., Dahlenburg, G W & Davis, J A. Changes in blood gas tensions following administration of amine buffer THAM to infants with respiratory distress syndrome. *Arch Dis Childh* 42:416 1967

20. Harrison, V.C., Heese, H. de V & Klein, M The significance f grunting in hyaline membrane disease *Pediatrics*, 41:549 1968

21 Karlberg, P Cook, C.D O'Brien D Cherry R.B. & Smith, C.A., Studies f respiratory physiology in the newborn infant. II Observations during and after respiratory distress. *Acta Paediat* 43.397 1954

22. Karlberg, P & Koch, G Respiratory studies in newborn infants. III Development of mechanics of breathing during the first week of lif A longitudinal study *Acta Paediat (Stockh)* Suppl 135.121 1962.

23 Klaus, M Tooley W.H Weaver K.H & Clements, J A. Lung volume in the newborn infant *Pediatrics*, 30.111 1962

24. Koch, G Henkanen, T Rähimaki, E., Lind J Tahti, E., & Österlund K. Regional distribution of ventilation and perfusion in th healthy newborn infant and in the idiopathic respiratory distress syndrome *Bull Physio-path resp* 9 1511 1973

25 Krauss, A.N & Auld, P.A.M Pulmonary gas trapping in premature infants. *Pediat Res*, 5.10 1971

26 Luft, U.C., Goddard R.F & Roorbach, E.H Characteristics f respiratory flow and pressures in newborn infants. *Feder Proc* 20.429 1961

27 Mead, J Control of respiratory frequency *J Appl Physiol*, 15.325 1960.

28. Mead, J & Agostoni, E. Dynamics of breathing. *I* W O Fenn & H Rahn (eds.) *Handbook of Physiology* American Physiological society W shington 1964 section 3 vol. 1 p 411

29 Miller, H.C. & Smull, N W Studies of respiratory insufficiency in newborn infants 1 Correlation of tidal and minute volumes with the trend f respiratory rates in premature infa ts *Pediatrics*, 19.224 1957

30. Nelson, N.M Prod'hom, L.S Cherry R.B Lipsitz, P.J & Smith, C.A Pulmonary function in the newborn infant. I Method Ventilation and gaseous metabolism. *Pediatrics*, 30:963 1962

31 Nelson, N.M Prod'hom, L S Cherry R.B Lipsitz, P.J & Smith, C.A. Pulmonary function in the newborn infant V Trapped gas in the normal infant s lung. *J Clin Invest*, 42 1850 1963

32. Otis, A.B Fenn, W.O & Rahn, H Mechanics of breathing in man. *J Appl Physiol*, 2:592, 1950.

33 Otis, A.B Mckerrow C.B Bartlett, R.A., Mead, J McIlroy M.B Selverstone N.J & Radford, E.P., Mechanical factors in distribution of pulmonary ventilation. *J Appl Physiol* 8:427 1956

34 Peterson, J H G & Pendleton, M.E. Contrasting roentgenographic pulmonary patterns of the hyaline membrane and fetal aspiration syndromes. *Am J Roentgen* 74:800, 1955

35 Polgar G & Strang, S T Th viscous resistance of the lung tissues in newborn infants. *J Pediat* 69.787 1966

36 Prod'hom L.S Levison, H Cherry R.B Drorbaugh, J.E., H bbell, J J.P & Smith, C.A., Adjustment of ventilation intrapulmonary gas exchange and acid-base balance during the first day of life. Normal values in well infants of diabetic mothers. *Pediatrics*, 33:682 1964

37 Prod'hom L.S Levison, H Cherry R.B & Smith, C.A., Adjustment f ventilation, intrapulmonary gas exchange and acid base balance during the first day of life Infants with early respiratory distress. *Pediatrics*, 35 662 1965

38. Reynolds, R.N & Etsten, B E. Mechanics f respiration in apneic nesthetized infants *Anesthesiology* 27.13 1966

39 Rudolph, A.J & Smith, C.A Idiopathic respiratory distress syndrome of the newborn. *J Pediat* 57:905 1960.

40. Schaffer A.J & Avery M.E. *Diseases of the newborn*. Saunders, Philadelphia, London Toronto 1971 3rd ed., p. 70

41 Selstam, U Karlberg, P & Olsson T Monitoring with impedance plethysmography in the neonatal period. *Acta Paediat Scand* Suppl 206 1970 p 22.

42. Snedecor G W & Cochran, W.G *Statistical methods*. The Iowa stat university press Ames, Iowa 1967 6th edition p 115

43 Sundell, H Garrott, J Blankenship W.J Shepard, F.M & Stahlman, M T Studies on infants with type II respiratory distress syndrome *J Pediat* 78 754 1971

44 Swyer, P.R., Reiman, R.C & Wright, J.J Ventilation and ventilatory mechanics in the newborn *J Pediat* 56:612, 1960

45 Thibeault D W Poblete, E & Auld P.A.M Alveolar-arterial O_2 and CO_2 differences and their relation to lung volume in the newborn *Pediatrics*, 41:574 1968

46. Victorin, L., Lindstrom D Sundell, H Talantos, A., Nrill, A.B & Stahlman M Positive end-expiratory pressure breathing in induced hyaline membrane disease (Abstract) *Pediat Res*, 7:426 1973

47 Wohl, M.E.B., Stigol, L.C. & Mead J Resistance of the total respiratory system in healthy infants and infants with bronchiolitis. *Pediatrics*, 43 495 1969

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IV WORK OF BREATHING

Ola Hjalmarson and Torsten Olsson

Introduction

The work of breathing in newborn infants with pulmonary disease is considered to be markedly increased (9 11 14 18). Cook et al. (11) commented from their measurements of the work of breathing in two infants with respiratory distress that their results supported "the clinical impression that these infants frequently die of exhaustion" and that therapy should, at least in part, be directed toward support of respiratory efforts If this is the case measurement of the work of breathing might be of clinical value, helpful in choice of therapy and an important parameter for monitoring in diseased infants. However to date only a limited number of observations have been reported on this topic.

Ventilation is a strong determinant of the work of breathing (24). In the previous section it was demonstrated that total ventilation was, on the average normal in infants with pulmonary disease and decreased below normal in infants with IRDS and low birth weight It has also been reported that breathing frequency and tidal volume were changed in an energy-saving direction (24). These findings suggest that only a limited increase in the work of breathing might accompany a reduced lung compliance On the other hand it was observed that a ventilation within the normal range occured in combination with an increased arterial P_{CO_2} This combination might have resulted from muscular insufficiency due to a heavy mechanical load.

Purpose of the study

This study was undertaken to examine the work of breathing in infants with pulmonary disease and to compare the work of breathing between healthy and diseased infants.

Concept and studies of work of breathing

Work of breathing is a complicated concept. Schematically the ventilatory system may be regarded from a mechanical point of view as two elastic units in series, the lung and the chest wall, respectively The chest wall comprises the rib cage diaphragm, abdomen and the abdominal wall. If no forces are applied the volume of the system is determined by the elastic properties of lung and chest wall. The muscles of breathing may change this equilibrium in any direction and change the volume of the system. This implies that mechanical work is done upon the system, the potential energy changes and energy is dissipated against resistances and in accelerating tissues and air in the system. Most of the work may be estimated from a volume-pressure-diagram if absolute pleural pressure during breathing is measured together with volume change and static compliance of the chest wall (6) However this measurement fails to include the work done in overcoming viscous resistance of the chest wall and the work encountered which produces deformation of the rib cage from its relaxed shape (6). Otis, Fenn and Rahn (24) presented a theoretical method to calculate work of breathing under the assumption that the time changes in the variables of breathing were sinus waves. Their results showed a satisfying fit to measured values. Cook et al. (11) modified the computations to suit a lung model with only one parameter of resistance and showed a good agreement between calculated and measured values newborn infants. This was also the case

15 Deming, J & Hamer, J.P Respiration in infancy II. A study of rate, volume and character of respiration in healthy infants during the neonatal period *Amer J Dis Child*, 51:823 1936

16 Drorbaugh, J.E., Segal, S., Sutherland, J.M Oppé, T.E., Cherry R.B. & Smith, C.A.. Compliance f lung during first week of life *Amer J Dis Child* 105:63 1963

17 Gluck, L. & Kulovich, M V Fetal lung development. Current concepts. *Pediat Clin N Amer* 20:367 1973

18 Griffin, A.J Ferrara, J.D Lax, J O & Cassels, D.E. Pulmonary compliance. *Amer J Dis Child* 123:89 1972.

19 Gupta, J M., Dahlenburg, G.W & Davis, J.A.. Changes in blood gas tensions following administration of amine buffer THAM to infants with respiratory distress syndrome. *Arch Dis Childh* 42 416 1967

20. Harrison, V.C., Heese, H de V & Klein, M The significance f grunting in hyaline membrane disease *Pediatrics*, 41:549 1968

21 Karlberg, P Cook, C.D O'Brien, D Cherry R.B & Smith, C.A. Studies of respiratory physiology in the newborn infant. II Observations during and after respiratory distress. *Acta Paediat* 43.397 1954

22. Karlberg, P & Koch G Respiratory studies in newborn infants. III Development of mechanics of breathing during the first week of life. A longitudinal study *Acta Paediat (Stockh)* Suppl 135.121 1962.

23 Klaus, M., Tooley W.H Weaver, K.H & Clements, J A. Lung volume in the newborn infant *Pediatrics*, 30.111 1962

24 Koch, H Hesikanen T Rikhmaki, E., Lind, J Tähti, E., & Österlund K. Regional distribution of ventilation and perfusion in the healthy newborn infant and in the idiopathic respiratory distress syndrome *Bull Physio-path resp*, 9.1511 1973

25 Krauss, A.N & Auld, P.A.M. Pulmonary gas trapping in premature infants. *Pediat Res*, 5.10 1971

26. Luft, U.C Goddard, R.F & Roorbach, E.H.. Characteristics of respiratory flow and pressures in newborn infants. *Feder Proc* 20:429 1961

27 Mead J Control of respiratory frequency *J Appl Physiol*, 15.325 1960

28 Mead, J & Agostoni, E. Dynamics of breathing. *In* W.O Fenn & H. Rahn (eds.) *Handbook of Physiology* American Physiological society Washington 1964 section 3 vol. 1 p 411

29 Miller H.C & Smull, N.W Studies f respiratory insufficiency in newborn infants 1 Correlation of tidal and minute volumes with the trend of respiratory rates in premature infants. *Pediatrics*, 19.224 1957

30 Nelson, N.M Prod'hom, L.S Cherry R.B Lipsitz, P.J & Smith, C.A. Pulmonary function in the newborn infant 1 Methods. Ventilation and gaseous metabolism. *Pediatrics*, 30:963 1962

31 Nelson, N.M., Prod'hom, L.S Cherry R.B Lipsitz, P.J & Smith, C.A Pulmonary function in the newborn infant. V Trapped gas in the normal infant lung *J Clin Invest*, 42.1850 1963

32. Otis, A.B Fenn, W.O & Rahn, H Mechanics of breathing in man *J Appl Physiol*, 2.592, 1950.

33 Otis, A.B., McKerrow C.B Bartlett, R.A., Mead, J McIlroy M.B Selverstone, N.J & Radford E.P Mechanical factors in distribution of pulmonary ventilation. *J Appl Physiol* 8:427 1956

34 Peterson, Jr H.C & Pendleton M.E. Contrasting roentgenographic pulmonary patterns of the hyaline membrane and fetal aspiration syndromes. *Am J Roentgen* 74:800, 1955

35 Polgar G & Strang, S T The viscous resistance of the lung tissues in newborn infants. *J Pediat* 69 787 1966

36 Prod'hom L.S., Levison, H Cherry R.B Drorbaugh, J.E., Hubbell Jr J.P & Smith, C.A.. Adjustment of ventilation, intrapulmonary gas exchange and acid-base balance during the first day of life Normal values in well infants of diabetic mothers. *Pediatrics*, 33:682, 1964

37 Prod'hom L.S., Levison, H Cherry R.B & Smith, C.A.. Adjustment of ventilation, intrapulmonary gas exchange and acid base balance during the first day f life Infants with early respiratory distress. *Pediatrics*, 35:662 1965

38. Reynolds, R.N & Etsten, B.E. Mechanics of respiration in apneic anesthetized infants. *Anesthesiology* 27.13 1966

39 Rudolph, A.J & Smith, C.A.. Idiopathic respiratory distress syndrome f the newborn. *J Pediat* 57:905 1960.

40. Schaffer A.J & Avery M.E. *Diseases of the newborn*. Saunders, Philadelphia, London Toronto 1971 3rd ed., p 70

41 Sekstam, U Karlberg, P & Olsson T Monitoring with impedance plethysmography in the neonatal period. *Acta Paediat Scand* Suppl 206 1970 p. 22.

42. Snedecor G.W & Cochran, W.G *Statistical methods*. The Iowa state university press Ames, Iowa 1967 6th edition p 115

43 Sundell, H Garrott, J Blankenship W.J Shepard F.M. & Stahlman, M T Studies on infants with type II respiratory distress syndrome. *J Pediat* 78 754 1971

44 Swyer P.R. Reiman, R.C. & Wright, J.J Ventilation and ventilatory mechanics in the newborn *J Pediat* 56:612 1960.

45 Thibeault D W Poblete E. & Auld, P.A.M Alveolar-arterial O_2 and CO_2 differences and their relation to lung volume in the newborn. *Pediatrics*, 41:574 1968

46. Victorin, L., Lindstrom D Sundell, H Tsiantos, A., Nnll, A.B & Stahlman, M Positive end-expiratory pressure breathing in induced hyaline membrane disease (Abstract) *Pediat Res*, 7:426 1973

47 Wohl, M.E.B Stigol, L.C & Mead J Resistance of the total respiratory system in healthy infants and infants with bronchiolitis. *Pediatrics*, 43 495 1969

compliance and/or high resistance the underestimation in relative terms, is smaller If expiration is active the underestimation of W_1 equals the hatched area in Figure 3 C. This is estimated from graphical plots to be 5–20 % of W_1 diminishing when loop area increases

Inspiratory activity during expiration in newborn infants

We first determined if as has been observed in adults (3) the infant relaxed the diaphragm during a portion of expiration.

Methods: Electromyographic recordings from the diaphragm were obtained from the region of cardia in esophagus by means of bipolar electrode. The electrode was fabricated from the ends of tw wires drawn through feeding catheter (nr 5) and fixed t 9 mm vertical distance at the outer uninsulated surface. The signals were fed into preamplifier and registered on polygraph (Mingograph 81). The electrode tube was introduced through nostril and pushed dow 15–20 cm into the esophagus. The position was then adjusted to give the best signal-to-noise ratio. Tidal volume as recorded by impedance plethysmography (23) or pneumotachography T test the assumption that the EMG activity recorded is representative for the entire diaphragm, EMG registrations and measurements of transdiaphragmatic pressure P_d were made simultaneously P_d was measured by means of tw esophageal balloons of type and properties previously described (section II) The balloons were introduced through the mouth and positioned in the ventricle, identified by pressure registration during breathing. One balloon as drawn back int the esophagus. The esophageal catheters er each connected to an identical pressure transducer (EMT 34) and pressure signals were recorded on the polygraph Bef re measurement both transducers ere calibrated against ter manometer and the deflexions were adjusted to be equal

Recording of esophageal pressure from healthy and diseased infants er studied ith special reference to the relation between the level of the esophageal pressure *during spontaneous apneas and the end expiratory level* during breathing.

Material Two newborn infants, birth weight 3190 g and 2900 g, without signs of disease were studied with EMG on the first day of life one hour after feeding One other infant, referred to as number 12 in Appendix (2130 g birth weight 34 weeks of gestational age) had idiopathic respiratory distress syndrome with typical lung roentgenogram and was studied at 21 hours of age Esophageal pressure recordings from one healthy infant and one infant with severe IRDS who later died, (number 9 in the Appendix) were also obtained.

Results and discussion. Parts of the EMG recordings are shown in Figure 4–6. In the healthy infant during the last part of expiration no EMG activity was detectable and the transdiaphragmatic pressure was constant (Fig. 4). The absolute transdiaphragmatic pressure includes pressure exerted by the esophageal walls and by mediastinal contents on the esophageal balloon. The absence of EMG activity implied that muscular work was absent. In the infant with IRDS the dominant pattern was an abscence of EMG activity during one part of expiration. EMG-activity was sometimes *seen also 40–50 ms before the onset of* inspiration.

The EMG results are in agreement with what was *observed from esophageal pressure recordings* during and around periods of apneas (Fig. 7 and 8). Pressures at end expiration approached those seen during apnea, indicating that relaxation volume is approximated at end expiration also in IRDS with high frequency of breathing. The end expiratory volume, as it appears in the continuous recording, is remarkably constant in the healthy sleeping infant as well as in the severly diseased one.

It is concluded that the basic pattern of breathing in healthy and diseased infants includes diaphragmatic relaxation during expiration. As a consequence it would be *possible to calculate the* major part of the work required to drive the lungs during the basic pattern in these infants.

Clinical study

W_A and W_R was calculated in 49 healthy newborn infants examined on 86 occasions and in 36 infants with pulmonary disease by one examination at or near the peak of their disease The infants are identical to those described in section III Results are given in terms of work required to overcome viscous resistance in the lung (W_R) and work required to drive the lungs (W_1) as estimated by W_A or if $W_R > W_A$ by W_R This estimation neglects W_B

Calculations of W_I

A) $W_A > W_R$

1) Breathing from relaxation volume (Fig. 3 A)

$$W_A = \int_0^{V_T} PdV = \int_0^{T} P\dot{V}dt.$$

P is esophageal pressure deviation from pressure at point A. V is volume deviation from starting volume. $\dot{V}$ is flow and T inspiratory time. Hence $W_I = W_A + W_B$

2) Breathing from higher lung volume (Fig. 3 B)
a) Inspiratory muscles acting during expiration. Expiration curve F' in Fig. 3 B. If the deviation from relaxation volume is ΔV_o, this means that an area ΔW_o, ADD"E in Fig. 3 B will be added to the total work.

$$\Delta W_o = \frac{V_T \Delta V_o}{C_l} + \frac{V_T \Delta V_o}{C_w} =$$

$$= V_T \Delta V_o \left(\frac{1}{C_l} + \frac{1}{C_w}\right)$$

C_l is lung compliance and C_w chest wall compliance.
Now $W_I = W_A + W_B + \Delta W_o$.
W_I is highly sensitive to ΔV_o. If ΔV_o is 10 % of V_T in a healthy newborn (C_l = 4 ml/ cmH_2O, C_w = 20 ml/cmH_2O, elastic work 70 % of W_A (19)), W_I is increased 15 %. If ΔV_o is 50 % of V_T the increase in W_I is 75 %. This means that W_I can not be calculated with any accuracy if ΔV_o is not small.

b) Inspiratory muscles relaxed during one part of expiration.
Fig. 3 B, expiratory curve F.
In this case pleural pressure during expiration will return to the line representing chest wall elastic pressure which means that W_R must increase. As far as $W_A > W_R$ the error in estimating W_I by W_A is limited and maximized by the area above curve F, under line DC and to the right of line DA in Figure 3 B.

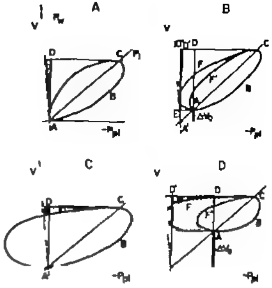

Fig. 3. Volume-pressure diagrams. See text.

B) $W_R > W_A$

1) Breathing from relaxation volume (Fig. 3 C)
$W_I = W_R$ + the hatched area in the figure. In active expiration the slope of the first part of the expiratory curve is seen to be slow and the hatched area small. In this study it was estimated from graphical plots to be 5–20 % of the loop area.

2) Breathing from higher lung volume (Fig. 3 D)
a) Inspiratory muscles relaxed during one part of expiration.
Expiratory curve F.
If W_I in this case is estimated by W_R it is underestimated by a quantity illustrated by the hatched areas in Figure 3 D, due to work done *during expiration by inspiratory muscles.* This underestimation is of limited importance as far as there is a phase of inspiratory muscle relaxation during the expiration.
b) Inspiratory muscles active during the whole expiration.
Expiratory curve F'.
$W_I = W_R$ + hatched + stippled area in fig. 4 D.
W_I can not be calculated from measurements made.

The finely-stippled area in Fig. 3 A can, however, not be measured during breathing. The measurable part of W_I is area ABCD, W_A. In the following this area is used to estimate W_I when expiration is passive which means an underestimation of W_I of about 10 %. In lung disease with low

breathing is in the results expressed per unit time i.e. work rate or power $\dot{W}_I$ with unit milliwatt mW. $\dot{W}_I$ is calculated from mean work per breath $\bar{W}_I$ in (ml) (cmH$_2$O) and breathing frequency f in min^{-1} with the formula

$$\dot{W}_I = 1.64\,\bar{W}_I\,f\ \ 10^{-3}$$

Statistics.

Group results are presented as means, S.D and range. Difference in variance among the groups was tested by F-test. The t-test was used to compare the means of groups with the same variances, and the method of Cochran (30 was used to compare means among groups with un equal variance. Regression lines and correlations were calculated by computer using standard formulae (30). From graphical plots log $\dot{W}$ was assumed to be normally distributed. Ninety-five per cent confidence intervals around the regression lines relating log $\dot{W}$ to log $\dot{V}_E$ were calculated as

$$\log \bar{\dot{W}} \pm t_{0.95}\ \ s_{\log \dot{W} \cdot \log \dot{V}_E} \sqrt{1+\frac{1}{n}}$$

where n is number of breaths per observation. For comparison of log W between groups at the same level of ventilation ventilation was adjusted to 1000 ml/min by using the regression coefficient calculated for healthy infants also for diseased infants. For comparison of W between groups in relation to body weight observations were compensated for differences in body weight using the calculated regression coefficient 0 70 mW/kg. Levels of confidence were assigned when $p<0.01$ and when $0.05>p>0.01$

Table 1 $\dot{W}_I$ and $\dot{W}_R$ in all groups of newborn infants, given in mW

Group	$\dot{W}_I$ Mean	S.D.	range	$\dot{W}_R$ mean	S.D	range
Reference group	4 9	2.3	1 0–13	4 3	2.5	5 13
IRDS	7.0	6.7	.63–[illegible]	5 0	5 2	20 23
Aspir. syndrome	10.8	7 4	18–26	10 3	7 7	65 26
Unclassified disorders	7.2	2.4	4 0–11	7 2	2.3	4 0 11

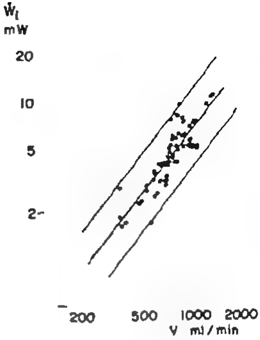

Fig. 9 Work rate related t ventilation in healthy infants. Regression line and 95 % confidence interval are marked

Results In 16 of 86 observations from healthy infants and in 17 of 36 diseased infants W_R was greater than W_I and calculation of $\dot{W}_I$ were based on W_R. Of the diseased infants, 5 of 18 with IRDS 6 of 11 with aspiration syndrome and 6 of 7 with unclassified disorders were of this type. $\dot{W}_I$ and $\dot{W}_R$ for all infants are shown in Table 1

As could be expected from the methods of calculation work rate was highly correlated to ventilation and pressure (Table 2). The regression of power on ventilation was nonlinear (Table 3) and plotted in Fig. 9. Table 2 also shows a positive correlation between $\dot{W}_I$ and W_R on one side and length and weight on the other. These correlations were partly dissolved if the significant positive correlation between ventilation and body size was considered as in Table 4

As the logarithmic values of W and V correlate to each other better than values on a linear scale the regression equations in Table 3 were used for standardizing values of power to a fixed level of ventilation.

In fig 10 the diseased infants are plotted with respect of ventilation and in fig 11 on w basis. The results for the different gro shown in Table 5. As demonstrated in T

Table 2. Correlations between $\dot{W}_I$ $\dot{W}_R$ and certain variables of ventilation in the reference group (from section III)

	$\dot{V}_E$	V_T	f	R_I	C_I	maxP_{in}	weight	length
$\dot{W}_I$	77	.54	25	25	08	71	.23	.31
log $\dot{W}_I$	.84	.56	28	22	13	70		
$\dot{W}_R$	72	48	.26	.35	13	.64	.21	.29
log $\dot{W}_R$	[illegible]	.51	30*	31	[illegible]	63		

Table 3 Regressions of log W_I and log W_R on ventilation V_E

log $\dot{W}_I$ 1.277 log $\dot{V}_E$ − 3.026

$S_{\dot{W}_I}$ $\dot{V}_E$ 0.124

log $\dot{W}_R$ = 1.564 log $\dot{V}_E$ − 3.943

$S_{\dot{W}_R}$ $\dot{V}_E$ 0.124

Table 4 Partial correlation coefficients relating W_I and W_R to weight and length with ventilation constant (n = 86)

	weight	length
$\dot{W}_I$	− 216	− 106
$\dot{W}_R$	−.216	107

.214 gives p .05 with 83 d f

Table 5 Log W_I and log W_R adjusted to a ventilation of 1000 ml/min in the different groups.

	log$\dot{W}_I$		log$\dot{W}_R$		
	mean	S D	mean	S.D.	n
Reference	805	124	749	124	86
IRDS	1 039	166	944	260	18
Aspir. syndrome	920	.208	876	232	11
Unclassified	867	167	877	197	7

7 $\dot{W}_I$ *in IRDS and aspiration syndrome* was higher than in the reference group at the same level of ventilation. W_I related to body weight, however was significantly increased only in aspiration syndrome Only three infants with IRDS showed a marked increase in W_I (Table 8). All these had relatively high birth weights and had high levels of ventilation in contrast to other infants with IRDS There were no significant differences between the unclassified group and the reference group but IRDS had a significantly higher work rate at the same level of ventilation. After recovery defined in page 27 and studied in the IRDS and aspiration syndrome groups no group differed significantly from reference values (*Table 10*) In crying the power of newborn infants was 25–50 times higher than the average for a quiet, healthy infant but also 4–9 times higher than the highest power seen in a diseased infant in this study (Table 9).

Discussion

Work rate of breathing is determined by the mechanical properties of the ventilatory system and the ventilation. Work rates for healthy infants in this study is somewhat higher than values reported by Cook et al (11) Karlberg and Koch (19) Swyer et al (33) and McIlroy and Tomlinson (22) (Table 11). The difference is explained by the lower compliance higher resistance and higher ventilation *found in this study* (see section III).

Work rate calculated for the crying infants does certainly not represent the maximum amount of work rate which the muscles of breathing are capable to produce as crying of this intensity very well may be continued for hours, but the values are interesting representing this state On the average work rates in the crying normal infants were *15–30 times higher* than those in infants with IRDS and 10–20 times greater than those in the aspiration syndrome group The high levels are explained by the high ventilation and the increased expiratory flow resistance during crying.

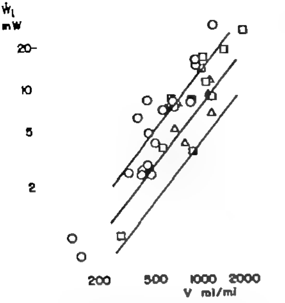

Fig. 10. Work rate related to ventilation in diseased newborns. Lines represent mean and 95 % confidence interval of healthy infants. ○ denotes IRDS, □ aspiration syndrome and △ unclassified lung disorders.

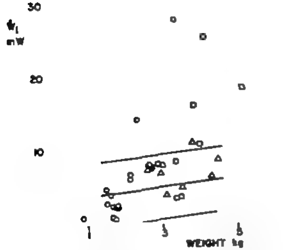

Fig. 11. Work rate related to body weight in diseased newborns. Lines represent mean and 95 % confidence interval of healthy infants. Symbols as figure 10.

When related to ventilation work rate is increased in both IRDS and aspiration syndrome as a sign of disturbed lung mechanics. When related to body size work rate is increased in the aspiration group but not in the IRDS group. This difference is explained by the difference in ventilation between these groups (see section III). Provided that the efficiency of the muscles of breathing is not changed our results implies that the metabolic cost to drive the lungs is not increased in IRDS.

The interpretation is in contrast with the previous hypothesis quoted in the introduction to this section. The difference is explained by differences in measured ventilation, which was high in the studies of Cook et al (11) and Karlberg et al (18). The lung disease of the infants in these studies were however less well defined. In the extensive study of Chu et al (9) in infants corresponding to those studied by us, total ventilation was not increased. The work of breathing was, however not measured but should agree with our results as lung mechanics in their infants were similar to ours.

The ventilatory system in adults is capable to increase its power 500 times from the basal state (24). This range in newborns is not known but the output may be increased at least 50 times during ordinary crying as was demonstrated in this study. In such a potent system, which under basal circumstances is responsible for only about one percent of the basal metabolic rate, more than a marginal increase in work rate must be expected before muscular exhaustion can be regarded as a probable cause of ventilatory insufficiency. This implies that even in the studies quoted the contribution of the work of breathing to mortality was insignificant. In infants with respiratory distress studied by Karlberg et al (18) and Scopes and Ahmed CO_2-production and O_2-consumption, respectively were normal, which is consistent with this theory.

The increase of $P_{A_{CO_2}}$ seen in some of the small infants with IRDS was not compensated for by increase of ventilation. This is evidently not due to a limitation of energy available to drive the lungs as the work rate of breathing was not increased. As a reduction of lung compliance leads to an increase of tension in lung tissues and in muscles of breathing at any lung volume this might be the basis for a feedback regulatory system to control the tidal volume. A reduction of tidal volume in IRDS, due to such a mechanism or another, is then not fully compensated by increase in breathing frequency in the severe immature infants. A breathing pattern

Table 2. Correlations between $\dot{W}_1$ W_R and certain variables of ventilation in the reference group (from section III)

	V_E	V_T	f	R_1	C_1	$maxP_{in}$	weight	length
$\dot{W}_1$	77	.54	25	.25	08	71	.23	.31
$\log \dot{W}_1$	84	.56	28*	.22	13	70		
$\dot{W}_R$	72	48	26	.35	13	.64	.21	.29
$\log \dot{W}_R$	82	.51	.30	31	18	63		

Table 3 Regressions of log W_1 and log W_R on ventilation V_E

$\log \dot{W}_1$ $1.277 \log V_E - 3\ 026$

$s_{\dot{W}_1\ V_E}$ $0\ 124$

$\log \dot{W}_R$ $1.564 \log V_E - 3\ 943$

$s_{\dot{W}_R\ V_E}$ $0\ 124$

Table 4 Partial correlation coefficients, relating W_1 and W_R to weight and length with ventilation constant (n = 86)

	weight	length
$\dot{W}_1$	–.216	– 106
$\dot{W}_R$	– 216	– 107

= .214 gives p = 05 with 83 d.f.

Table 5 Log W_1 and log $\dot{W}_R$ adjusted to a ventilation of 1000 ml/min in the different groups.

	$\log \dot{W}_1$		$\log \dot{W}_R$		
	mean	S D.	mean	S.D.	
Reference	805	124	749	124	86
IRDS	1 039	166	944	.260	18
Aspir.syndrome	920	.208	876	.232	11
Unclassified	.867	167	.877	197	7

7 $\dot{W}_1$ in IRDS and aspiration syndrome was higher than in the reference group at the same level of ventilation. $\dot{W}_1$ related to body weight however was significantly increased only in aspiration syndrome. Only three infants with IRDS showed a marked increase in W_1 (Table 8) All these had relatively high birth weights and had high levels of ventilation in contrast to other infants with IRDS. There were no significant differences between the unclassified group and the reference group but IRDS had a significantly higher work rate at the same level of ventilation. After recovery defined in page 27 and studied in the IRDS and aspiration syndrome groups no group differed significantly from reference values (Table 10). In crying the power of newborn infants was 25–50 times higher than the average for a quiet, healthy infant but also 4–9 times higher than the highest power seen in a diseased infant in this study (Table 9).

Discussion.

Work rate of breathing is determined by the mechanical properties of the ventilatory system and the ventilation. Work rates for healthy infants in this study is somewhat higher than values reported by Cook et al (11), Karlberg and Koch (19) Swyer et al (33) and McIlroy and Tomlinson (22) (Table 11) The difference is explained by the lower compliance higher resistance and higher ventilation found in this study (see section III).

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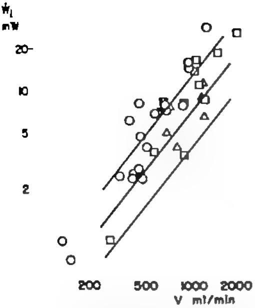

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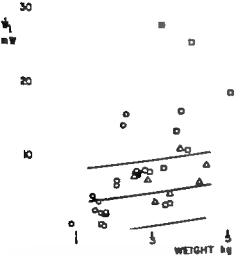

Fig. 11. Work rate related to body weight in diseased newborns. Lines represent mean and 95 % confidence interval of healthy infants. Symbols as figure 10.

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Table 6. Differences in log W_l in mW between groups, their t-values, degrees of freedom (d.f.) and level of significance at 1000 ml total ventilation per minute

	Reference			IRDS			Aspir. syndrome		
	Diff	t	d.f	diff	t	d.f	diff.	t	d.f
IRDS	.234	6.84	102	–	–	–	–	–	–
Aspir.syndrome	.115	2.72	95	.119	.575	27	–	–	–
Unclassified	.062	1.22	91	.172	2.32	23	.053	.567	[illegible]

Table 7. Differences in W_l in mW between clinical groups adjusted for body weight, t and t' [1] values and levels of significance

	Reference		IRDS		Aspir. syndrome	
	Diff		Diff		Diff.	
IRDS	2.5	t' 1.52				
Aspir.syndrome	5.3	t' = 2.38	2.8	t 1.06 (27 d.f.)		
Unclassified	1.7	t 1.86 (91 d.f.)	.8	t .29 (23 d.f.)	–3.6	t 1.23 (16 d.f.)

[1] calculated according to Cochran (30)

Table 8. Data on 3 infants with IRDS and increased W_1 in relation to body weight.

Pat. number [1]	weight g	gest.age weeks	age days	V ml/min	f min⁻¹	O_2% inspired	Pa_{O_2} mmHg	P_{CO_2} [2] mmHg	duration of O_2 therapy days	lung X-ray
2	2280	35	1.0	1050	97	56	47	a54	6	reticulogranular+ air bronchogram
14	3360	38	1.3	1390	131	56	48	a30	6	suspect reticulo-granular on right side
[illegible]	2390	36	7	1040	136	28	not mea-sured	v43	5.5	discrete, suspect reticulogranula-rity

[1] see appendix
[2] a arterial, v venous

Table 9. Work rate in 3 healthy crying infants.

Weight g	age days	V ml/min	$\dot{W}_l$ mW
2400	[illegible]	2680	110
440	1	3030	230
3190	7	2740	200

Table 10. $\dot{W}_l$ after recovery compared to healthy infants.

		$\dot{W}_l$ mean	S.D
Reference group	49	4.9	2.2
IRDS	[illegible]	4.8	3.1
Aspiration syndrome	8	7.1	3.7

Table 11 Work rate in milliwatt (mW) in healthy newborn infants from different studies.

Study		weight g	ventilation ml/min	W mW	mode of calculation
McIlroy and Tomlinson (22)	7	3.3	578	4.3 (1.8–8.5)	measurements in pV-diagram ?
Cook et al (11)	10	3.0	610	2.3	Formula of Otis, Fenn and Rahn (24)
Swyer et al (33)	15	3.0	730	3.4 (1.6–6.0)	0.6 PV (11)
Present data	86	2.7	790	4.9 (1.0–13.0)	see text

tidal volumes but increased frequency is meaningful as a way to reduce the work of breathing at any ventilation level when lung compliance is reduced.

In conclusion

The amount of work rate of breathing in the diseased infants studied was either increased or not different from healthy infants. In relation to ventilation, work rate of breathing was increased in IRDS and aspiration syndrome indicating disturbed lung mechanics. The total amount of work rate of breathing in IRDS was not increased in contrast to what is generally postulated. It is concluded that the work of breathing does not contribute significantly to the outcome of IRDS

REFERENCES

1. Agostoni, E. Volume-pressure relationships of the thorax and lung in the newborn. *J Appl Physiol*, 14:909 1959
2. Agostoni, E. & Mead, J. Statics of the respiratory system. In W.O. Fenn & H. Rahn (ed.): *Handbook of physiology*. American Physiological society. Washington 1964 section 3 vol. I p. 387
3. Agostoni, E. Action of the respiratory muscles. *In* W.O. Fenn & H. Rahn (ed.): *Handbook of physiology*. American Physiological Society. Washington 1964 section 3 vol. I p. 377
4. Agostoni, E. Mognoni, P. Torri, G. & [illegible], G. Forces deforming the rib cage. *Resp Physiol*, 2:105 1966
5. Agostoni, E., Campbell, E.J.M. & Freedman, S. Energetics. *In* E.J.M. Campbell, E. Agostoni & J. Newsom Davis: *The respiratory muscles*. Lloyd-Luke, London, 1970 2nd ed., p. 121
6. Agostoni, E., Campbell, E.J.M. & Freedman, S. Energetics. *In* E.J.M. Campbell, E. Agostoni & J. Newsom Davis: *The respiratory muscles*. Lloyd-Luke, London, 1970, 2nd ed., p. 115
7. Avery, M.E. & Cook, C.D. Volume-pressure relationships of lungs and thorax in fetal, newborn, and adult goats. *J Appl Physiol*, 16:1034 1961
8. Berglund, G. & Karlberg, P. Determination of the functional residual capacity in newborn infants. Preliminary report. *Acta Paediat Scand*, 45:541, 1956.
9. Chu, J., Clements, J.A., Cotton, E.K., Klaus, M.H., Sweet, A.Y. & Tooley, W.H. Neonatal pulmonary ischemia. Part I. Clinical and physiological studies. *Pediatrics*, 40:709 1967
10. Cook, C.D., Cherry, R.B., O'Brien, D. Karlberg, P. & Smith, C.A. Studies of respiratory physiology in the newborn infant. I. Observations on normal premature and full-term infants. *J Clin Invest*, 34:975 1955
11. Cook, C.D. Sutherland, J.M., Segal, S., Cherry, R.B., Mead, J., McIlroy, M.B. & Smith, C.A. Studies of respiratory physiology in the newborn infant. III. Measurement of mechanics of respiration. *J Clin Invest*, 36:440, 1957
12. Ferris, Jr. B.G., Mead, J. & Opie, L.H. Partitioning of respiratory flow resistance in man. *J Appl Physiol*, 19:653 1964
13. Gerbeaux, F. & Senterre, J. Method of investigation of the mechanics of breathing in the artificially ventilated newborn. *Biol Neonate* 16:35 1970
14. Gregg, R.H. & Bernstein, J. Pulmonary hyaline membranes and the respiratory distress syndrome. *Amer J Dis Child* 102:871 1961
15. Gregory, G.A., Kitterman, J.A., Phibbs, R.H. Tooley, W.H. & Hamilton, W.K. Treatment of IRDS with continuous positive airway pressure. *N E Med* 284:1333 1971

16. Harrison, V.C., Heese H. de V & Klein, M., The significance f grunting in hyaline membrane disease. *Pediatrics*, 41:549 1968
17 Jonsson, B & Olsson, L.G. Measurement f the work f breathing to overcome pulmonary viscous resistance. *Scand J clin Lab Invest* 28 135 1971
18 Karlberg, P Cook, C.D O'Brien, D Cherry R.B. & Smith, C.A.. *Studies f respiratory physiology in the* newborn infant. II. Observations during and after respiratory distress. *Act Paediat* 43.397 1954
19 Karlberg, P & Koch, G Respiratory studies in newborn infants. III Development of mechanics of breathing during the first week of life. A longitudinal study *Acta Paediat (Stockh)* Suppl 135 121 1962.
20. Konno K. & Mead J.. Measurement of the separate volume changes of rib cage and abdomen during breathing. J Appl Physiol, 22:407 1967
21. Margaria, R., Milic Emili, G., Petit, J.M & Cavagna, G. Mechanical work of breathing during muscular exercise. *J Appl Physiol*, 15.354 1960.
22. McIlroy M.B & Tomlinson, E.S. The mechanics f breathing in newly born babies. *Thorax, 10:58 1955*
23 Olsson, T & Victorin, L.. Transthoracic Impedance, with special reference to newborn infants and the ratio air-to-fluid in the lungs. *Acta Paediat Scand* Suppl 207 1970
24 Otis, A.B., Fenn, W O & Rahn, H. Mechanics of breathing in man. *J Appl Physiol*, 2:592, 1950.
25 Peterson, Jr H G. & Pendleton, M.E. Contrasting roentgenographic pulmonary patterns f the hyaline membrane and fetal aspiration syndromes. *Am J Roentgen*, 74:800, 1955
26. Prod'hom, L.S., Levison, H., Cherry R.B. & Smith, C.A.. Adjustment of ventilation, intrapulmonary gas exchange, and acid base balance during the first day of life. Infants with early respiratory distress. *Pediatrics*, 35.662, 1965
27 Reynolds. R.N & Etsten, B.E.. Mechanics of respiration in apneic anesthetized infants. *Anesthesiology* 27 13 *1966*
28. Richards, C.C. & Bachman, L. Lung and chest wall compliance of apneic paralyzed infants. *J Clin Invest*, 40:273 1961
29 Scopes, J W & Ahmed, I Minimal rates of oxygen consumptio in sick and premature newborn infants. Arch Dis Childh, 41 407 1966.
30. Snedecor G W & Cochran, W G., *Statistical methods*. The Iowa state university press, Ames, Iowa 1967 6th edition, p 115
31. Strang, L.B. & MacLeish, M.H. Ventilatory failure and right to-left shunt in newborn infants with respiratory distress. *Pediatrics*, 28 17 1961
32. Sundell, H., Garrott, J Blankenship W.J., Shepard, F.M. & *Stahlman M.. Studies* on *infants with type II* respiratory distress syndrome. *J Pediat*, 78.754 1971.
33 Swyer P.R., Reiman, R.C. & Wright, J.J Ventilation and ventilatory mechanics in the newborn. *J Pediat*, 56:612, 1960
34 Wohl. M.E.B., Stigol, L.C. & Mead, J Resistance of the total respirator system in healthy infants and infants with bronchiolitis. *Pediatrics* 43-495, 1969

V CLINICAL APPLICATION OF MEASUREMENTS OF MECHANICS OF BREATHING

It is difficult to assess the risk for the infant when a neonatal lung disease first appears. The disease may develop rapidly during the first hours of life run a transient course or turn to a severe life-threatening disease which calls upon large resources in trained personnel and special equipment. The clinical picture is however seldom pathognomonic for any lung disease but may be imitated for example by cardiac malformations and central nervous system disturbances. In this situation the clinician requires techniques for fast and reliable diagnosis. Clinical picture lung x-ray and blood gas analyses are helpful tools and are in most cases good enough to meet the requirements mentioned. However early stages of different diseases including disturbances originating from purely immature lung, infection and intracranial bleeding are often not easy to differentiate. In these cases there is a definite need for methods for functional examination of the lungs. This study has been concerned with mechanics of breathing for these purposes.

In the previous section it was demonstrated that mechanics of breathing can be studied even in severely diseased infants without hazards. Accurate results require that a number of sources of error are controled by elimination or compensation. The practical possibilities to work with such a system is increased if a computer is used. Its capacity for computations may also be used for calculation of other parameters than the ordinary resistance and compliance.

In the following some main findings with relevance for clinical work are summarized together with some aspects on monitoring of mechanical parameters.

Studies during the acute phase of the disease

Dynamic lung compliance. Lung compliance is determined not only by elastic recoil of the lung but also by several other factors and was in this study regarded as an index of mechanical lung disturbance (page 23). With respect to compliance the diseased infants separated into three groups representing different degrees of lung involvement in this respect

a) Low compliance during more than one day
b) Low compliance at only one occasion
c) Compliance not reduced

The infants with longstanding mechanical lung disturbance (group a) were clinically infants with IRDS. Infants with a more transient mechanical lung disturbance had either aspiration syndrome or belonged to the group of unclassified disorders. Infants without reduction of compliance were also found in either the aspiration syndrome or the unclassified group.

The differentiation between the first two categories of lung involvement is clinically important and the difference is clearcut in serial compliance measurements. In this study x-ray pattern of definite or suspect reticulogranularity and air bronchogram will identify the same population as category a above. A special interest may be directed to C_1/C_2-ratio implying non-linear mechanical parameters in the lung model chosen (page 22). The ratio is distinctly higher in IRDS than in healthy infants. Even in infants with aspiration syndrome this ratio is elevated but seems to be lower than in IRDS. The groups of diseased infants studied are however still too small for the difference to reach statistical significance.

More data is required to determine if infants with a transient reduction of compliance are clinically or pathophysiologically uniform and distinct from the diseased infants without any reduction of lung compliance.

It cannot be established from available data if mechanisms responsible for a low [illegible] differ from one disease to [illegible]

studied There is, however no evidence that the degree of right to-left shunt in general is reflected by the level of lung compliance per se measured as compliance was reduced also in infants with aspiration syndrome where no infant required more than 34 % oxygen in inspired air and hence shunted in considerably less degree Nor is lung compliance related to the degree of lung involvement seen in the lung radiogram when compared between different kinds of abnormalities, as it was evident in the study presented that non-IRDS-infants with large opacities on the lungs might have normal lung compliance. In infants with reticulogranular pattern on chest radiograms the course of the disease in terms of requirement of oxygen, however roughly parallelled the changes in compliance

Conclusion. Lung compliance and C_1/C_2 were shown to differentiate between individuals with neonatal lung disease in a way that can be clinically useful.

Lung resistance measured was very variable in the material. The variation was obviously much more due to closure of the vocal cords or the glottis than to processes within the lung. In grunting, not always possible to hear without a stethoscope but visible on flow record lung resistance usually was high. In infants below 2000 g with lung disease high lung resistance was seen only in connection with reduced lung compliance and reticulogranular pattern on lung x ray Except for in this combination seen in some cases lung resistance seems to be of limited value for diagnosis in the group of infants studied but this certainly does not hold for all kinds of respiratory distress in the newborn period

Ventilatory adjustments

There is a clear tendency to have an increased frequency and a decreased tidal volume at low lung compliance This is consistent with the theory of the regulation of the breathing pattern in an energy saving direction (5) The total ventilation is however decreased in the small infant with IRDS in spite of an increased Pa_{CO_2} This may imply a change in the central nervous regulation of breathing in this category of infants. The increased breathing frequency in IRDS infants is generally not an expression for an increased ventilation but for an adjustment of the breathing to a more economical pattern (5)

Work of breathing. The clinical significance of the results of the measurements of work of breathing in section IV must be interpreted with some caution. Although the work rate of breathing was in general moderately increased in relation to ventilation it was within the 95 % confidence interval of healthy infants when related to body size in most IRDS infants, due to a decreased ventilation Measurements of work of breathing in this study do not give support to the conception that muscular exhaustion is a primary cause of death in infants with IRDS. It is, however not known if the working capacity of the muscles of breathing is intact but the good results from therapy with continous distending pressure (CDP) (2) may indicate that it is the case In infants with aspiration syndrome the work rate was in general increased at ordinary or increased ventilation.

In IRDS right-to-left shunting is a primary problem and the cause of the hypoxia in this disease (7). There is no evidence that hypoxia is caused by a general ventilatory insufficiency Major increase of Pa_{CO_2} is a terminal event (1). These facts suggest that ventilator therapy should be restricted to infants with increased P_{CO_2} In others as well as in infants under ventilator treatment therapy should be primarily directed to diminish the right to-left shunt, i.e by CDP Results achieved in IRDS infants ventilated without CDP for low Pa_{O_2} are not always bad, however (4) In a situation when evidence of a significant increase of the work of breathing is lacking it is reasonable to suggest that the positive results may indicate an effect on the right-to-left shunt exerted by intermittent positive pressure ventilation. Results of Reynolds et al (3 6) in studies of the effect of alteration of ventilator settings in infants with IRDS may indicate the existence of such a mechanism.

Monitoring

One purpose of this study was to evaluate the mechanical lung parameters and the work of breathing for purposes of monitoring. In IRDS reduction of *lung compliance* seems to roughly

parallell the requirements of extra administered oxygen during the disease and lung compliance seems to be the best conventional parameter to follow during the course of that disease

During the planning of the study *work rate of breathing* was considered interesting to follow as an indicator of the need of ventilatory therapy because of its expected relation to muscular exhaustion. As demonstrated work rate of breathing measured was lower in the group known to have the highest mortality (IRDS) than in the more benign groups, and not significantly differing from healthy infants with the same body weights. This shows that work rate is not a suitable monitoring parameter in the diseases studied.

Another parameter however seems promising for diagnosis of mechanical disturbances of the lung. As an effect of disturbed mechanics of breathing changes can be observed in the ratio between the ventilatory flow and the pleural pressure driving in lung. An expression of this ratio which is an analogue to electrical "admittance" was presented on page 18 calculated over the inspiratory phase. Admittance is an expression of the ability of the ventilatory apparatus to transform pleural pressure to ventilatory flow The expression does not apply any assumptions on the mechanical behaviour of the lung. If the mechanical properties of the lung are changed by increase of resistance or decrease of compliance admittance will be reduced. This reduction might be used as

Fig 1 Lung admittance in healthy newborns (black dot) and in newborns with pulmonary disease ○ denotes IRDS □ aspiration syndrome and △ unclassified lung disorders (see section III)

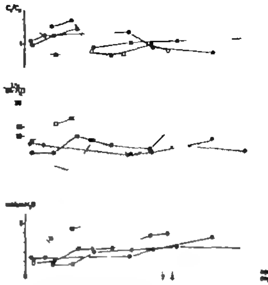

Fig. 2. C_1/C_2, lung admittance and dynamic lung compliance measured during the course of the disease in three infants with IRDS (circles) and in two infants with aspiration syndrome (squares).

a sign of mechanical disturbances of the lung. As flow changes with body weight, admittance is expected to be correlated to body weight. Figure 1 shows admittance in relation to body weight in the healthy and diseased infants described in section III. There is a good separation between healthy and diseased infants below 3 kg. As the infants with low admittance are those who from a clinical point of view constitute the high risk group measurement of lung admittance may be a valuable index in diagnostics and for monitoring.

In Figure 2 C_1/C_2 and lung admittance are plotted for some infants with IRDS and aspiration syndrome in the course of the disease Changes in C_1/C_2 and lung admittance parallells, in these cases, the changes in lung compliance IRDS infants showed a first phase with increasing C_1/C_2 followed by an abrupt fall to the levels of healthy infants (Table 16 page 43) Much the same changes, but in inverse direction, were seen in admittance. One of the infants with aspiration syndrome had entirely normal C_1/C_2 but demonstrated a fall in admittance parallell to a fall in lung compliance

In conclusion, measurement of different aspect mechanics of breathing in newborn

clinical significance for assessment of diagnosis, underlying pathophysiology and for following of a dynamic clinical course in neonatal pulmonary disease

REFERENCES

1 Chu J Clements, J.A., Cott n, E.K., Klaus, M.H., Sweet, A.Y & Tooley W.H. Neonatal pulmonary ischemia. Part I Clinical and physiological studies. *Pediatrics*, 40 709 1967

2. Gregory G.A., Kitterman, J.A., Phibbs, R.H Tooley W.H. & Hamilton, W.K. Treatment of IRDS with continuous positive airway pressure. N Engl J Med, 284.1333, 1971.

3. Herman, S. & Reynolds, E.O.R.. Methods for improving oxygenation in infants mechanically ventilated for severe hyaline membrane disease *Arch Dis Child*, 48:612 1973

4. Karlberg, P & Kjellmer I Treatment of respiratory distress in the newborn infant. *Bull Physio-path resp* 9.1601 1973

5 Otis, A.B., Fenn, W.O. & Rahn H. Mechanics of breathing in man. *J Appl Physiol*, 2:592 1950

6 Reynolds, E.O.R. Effect f alterations in mechanical ventilation settings on pulmonary gas exchange in hyaline membrane disease. *Arch Dis Childh*, 246 152, 1971

7 Strang, L.B. & MacLeish, M.H. Ventilatory failure and right-to-left shunt in newborn infants with respiratory distress. *Pediatrics*, 28 17 1961

ACKNOWLEDGEMENTS

I am deeply grateful to my teacher Professor Petter Karlberg who guided me into the field of mechanics of breathing. His neverfailing interest, support and advice made this work possible. My sincere thanks are also due to Docent Ingemar Kjellmer for his deep interest, encouragement and readiness and willingness to penetrate problems and give advice throughout the study and during the preparation of the manuscript. Dr Harry Larsson spent many hours in front of the x rays of this study and gave me rich possibilities to learn from his vast experience. To his interest and much work in this study I am deeply indebted. I am grateful to Professor Henry Wallman and Assist. Professor Jerry Dempsey for valuable discussions and for help with the English language For invaluable help with skillfull technical assistance I am indebted to Mrs Elna Zetterberg. The valuable help with curves and graphs by Mrs Eva Hermansson is gratefully acknowledged. Finally I wish to thank all members of the staff of the neonatal unit for all their help throughout this work.

This work was supported by grants from
The Swedish Board for Technical Development
reg. number 733764
The First of May Flower Annual Campaign for Children s Health
The Medical Faculty University of Goteborg
Göteborgs Barnsjukhus Forskningsfond and
The Fels Research Institute for the study of Human Development Yellow Springs, Ohio

APPENDIX

Climical, ventilatory and mechanical parameters obtained during pulmonary disease and after re covery in newborn infacta.

Patient number, Delivery, Apgar score	Age days	gest. age week	Weight gram	length cm	R cmH$_2$O/l/s	C ml/cmH$_2$O	V_{TG} ml	V_T ml	max $\dot{V}_{in}$ ml/s	max $\dot{V}_{ex}$ ml/	max P_{in} cmH$_2$O	max P_{ex} cmH$_2$O	f /min	$\dot{V}_E$ ml/min	F_IO_2 %	Dur O_2 days	pH	pCO_2 mmHg	pO_2 mmHg	Comments	X-ray	Diagnosis
1	0.4	30	1750	41	38	0.70	3	5.2	33	29	7.8	0.9	91	470	60/48	3.7	7.24	75			Ret.gran.	IRDS
	1.4		1630	41	37	0.71	37	3.1	14	10	4.9	0.7	49	160	40		7.30	v54	—		0	
Duplex	2.4		1630	41	48	2.1	35	6.0	36	22	3.8	0.8	67	400	26		7.30	v52				
(Apg. 9)	4.2		1520	42	42	2.4	16	8.1	28	14	4.2	1.0	48	330								
	8.4		1430	42	39	2.7		7.6	32	30	3.8	1.0	55	420								
	15.4		1640	43	52	2.6	52	11.3	38	34	5.3	2.7	43	490								
	21		1800	43.5	35	3.6		7.8	30	25	2.6	0.9	54	420								
	30		1930	44	41	1.9	107	15.3	47	40	9.2	1.6	50	770								
	36		1970	44.5	57	2.4	61	13.8	43	48	7.0	1.1	46	630								
2	1.6	30	1790	43	77	0.49	0	5.4	33	25	6.9	0.4	75	400	60/44	8	7.27	v60			Ret.gran.	IRDS
	2.6		1760	43	62	0.57		4.9	33	21	11.0	0.9	65	350	/40		7.24	a40	63		Ret.gran.	
Duplex	8.7		1550	44	52	2.1	71	8.8	35	27	5.1	1.1	48	420	/26							
(Apg. 9)	9.4		1550	44	56	2.0		7.6	28	23	4.6	0.6	47	360								
	16**		1600	45	86	2.1		9.8	34	27	6.3	1.2	50	400								
	22		1800	44	115	1.0	37	12.8	48	35	14.3	2.7	48	620								
	36		2070	46	80	1.8		14.4	45	28	9.6	1.8	37	530								
3 Sectio	0.1	33	2620	47.5	125	1.0	102	8.7	60	75	8.4	8.6	56	400	60/34	6	7.26	a47	97		Ret.gran+ PT+PM	IRDS
(placenta	5		2200	47.5	58	2.0	50	13.6	56	37	7.8	1.3	56	700	35							
praevia)	7*		2260	47.5	54	3.1		15.3	59	30	6.7	1.6	37	570							Reduced air dx	
(Apg. 9)	12		2300	48	83	3.8		12.8	53	33	6.7	1.4	46	590								
	18		2620	47.5	63	3.2	64	17.4	58	44	8.1	1.4	50	870								
4 Sectio	2.4	34	1630	44	51	0.99		8.0	46	35	9.1	1.2	67	550	60/50	9	7.28	a43	60		Ret.gran.	IRDS
(placenta	9		1410	44	54	3.0	70	12.2	43	27	5.4	1.6	39	470	/30		7.34	a34	108			
praevia	18*		1590	45	77	2.8		13.6	53	28	7.0	1.8	42	640							0	
duplex)	24		1660	46	90	2.3		16.9	38	34	9.6	1.9	49	820								
(Apg. 1)	30		1870	46.5	19	4.3	93	14.7	64	71	4.2	0.9	38	560								
5 Normal (Apg. 5)	0.2	<28	810	37	115	0.41		3.0	14	20	7.5	2.4	43	130	58/48	0.3	7.17	a66	42	Died 0.3 d	Ret.gran.	IRDS
6 Sectio	0.4	35	2340	43	29	1.6	31	10.6	77	61	7.1	0.7	105	1110	58/40	6	7.28	a60	60		Ret.gran.	IRDS
(Diabetes	0.9		2200	43	27	0.80		9.9	76	73	13.4	1.2	116	1130	/44		7.31	a49	33			
mellitus	1.0*		2200	43	29	0.73		11.2	75	82	16.5	2.1	97	1000	/56		7.26	a54	47		Ret.gran.	
matris)	4.2		2300	43	34	1.1	80	7.5	56	46	7.7	1.0	84	630	/36		7.32	a54	76			
(Apg. 9)	5		2070	44	139	1.3	15	11.0	47	40	12.2	4.1	62	690							0	
	15		2160	44	43	3.6	93	16.0	59	46	3.7	0.9	46	730								
	23		2340	45	47	3.9	107	10.3	74	61	5.2	2.2	33	600								

7	0.4	35	1750	7	37	0.83	64	5.6	37	39	7.1	0.9	79	30	50/50	2.3	7.1	a58	00		Ret gran.	IRDS
Sectio	2.2		1720	[illegible]	[illegible]	1.6		7.3	[illegible]	[illegible]	3.6	1.3	[illegible]	640	24		7.33	a41	97		0	
(placenta praevia+ [illegible])	20**		1770	48	39	4.6		23.2	[illegible]	43	6.4	1.6	[illegible]	1240								
(Apg. 4)																						
8	0.8*	36	1680	43	[illegible]	1.2	52	6.2	45	36	6.2	[illegible]	82	510	40/40	3	7.31	a43	51		Ret gran.	IRDS
Normal	1.6		1730	43	29	1.9	77	[illegible]	56	43	4.8	[illegible]	99	810	/[illegible]						0	
	8**		1720	[illegible]	33	2.3		13.2	[illegible]	34	5.7	1.1	44	590								
(Apg. 2)	16		1920	43	95	3.3	133	6.2	56	41	8.3	2.0	46	720								
9 (Apg. 6)	[illegible]	[illegible]	1400	[illegible]	70	0.40	39	4.3	36	35	11.0	1.4	82	490	46/46	1.0	7.26	a51	73	Dead 1.0 d	Ret gran.	IRDS
10	0.3	36	2550	47	31	1.4	71	11.8	61	87	8.9	1.4	114	1350	60/40	7	7.28	a42	50		Ret gran.	IRDS
Normal	1.0*		2575	47	32	1.4		9.4	62	65	7.4	1.3	105	980	/50		7.38	a33	[illegible]		Ret gran.	
	5.3		2390	47	56	1.8	113	9.3	47	47	7.2	1.2	78	720	/40		7.29	a40	73			
(Apg. 10)	[illegible]		2500	47	[illegible]	2.5		9.8	[illegible]	26	5.1	1.3	52	460	/30						Pneumonia-[illegible]	
	12**		2440	48	36	3.7	64	14.4	50	36	5.2	0.9	46	660								
11	0.3	36	2730	47	48	1.0	27	7.7	52	33	8.9	0.9	95	730	30/30	3.5	7.27	a49	80		Ret gran.	IRDS
Partial	5		2310	[illegible]	68	3.4	119	9.3	25	30	4.1	1.2	48	440							0	
ablatio placentae	13**		2730	47	60	4.1	150	20.0	88	56	8.3	1.9	57	1120								
(Apg. 9)																						
12	0.3*	34	2130	46	86	0.9	29	9.9	85	63	12.2	5.4	64	630	90/90	9	7.15	a64	195		Ret gran.	IRDS
Sectio	3		2130	46	43	1.2	41	9.8	56	41	9.7	2.0	64	430	/40		7.15	a56	54		Regress	
(Apg. 5)	10*		2850	49.5	90	3.6	54	21.4	77	77	8.4	1.8	51	1100							0	
13	0.4*	[illegible]	2700	47	27	0.80		6.8	65	49	9.6	0.9	102	750	30/30	2.3	7.36	a48	50		Ret gran?	IRDS?
	[illegible]		2700	47	[illegible]	1.2		9.6	79	65	9.1	1.4	125	1200	/30		7.32	a42	65			
Normal	1.5		2720	47	[illegible]	1.1		9.6	41	41	9.0	1.4	84	800	/[illegible]				63			
	2.7		2610	47	[illegible]	2.4		10.5	53	34	5.1	1.0	60	630								
(Apg. 10)	3.4		2520	[illegible]	40	4		9.7	48	28	4.8	2.0	61	600								
	4		2400	[illegible]	30	2.6		14.0	63	47	7.6	1.3	60	830								
	6.4		2490	[illegible]	37	3.9		12.8	29	16	3.9	[illegible]	29	770								
	7.3		2500	48	39	4.1		16.7	39	56	5.2	1.5	[illegible]	780							0	
	8.3		2780	48	39	4.1		12.1	[illegible]	40	3.8	0.8	42	520								
14	0.3	38	3350	49	64	0.88	33	7.1	45	62	9.6	1.7	154	1090	60/38	6		a40	51		Ret gran?	IRDS?
Normal	1.3		3360	9	68	0.68	0	11.0	101	[illegible]	17.6	2.3	131	1430	/46						Ret gran.	
(Apg. 10)	8		3020	49	40	3.4	87	16.2	65	43	6.0	0.5	[illegible]	610							dx	
	[illegible]		3050	9	113	3.0	153	18.3	[illegible]	37	8.8	3.6	[illegible]	770							0	
15	0.7*	36	2390	44	33	0.58	27	7.8	61	60	14.7	0.9	136	1070	32/28	5.5	7.29	v43			Ret gran	IRDS?
Normal	2.4		2430	44	8.2	1.0	70	10.0	95	117	10.3	1.1	118	1170	32		7.36	k43			+small [illegible]	
(Apg. 9)	5.3		2190	44	[illegible]	2.5	107	[illegible]	56	66	4.3	0.9	59*	530	[illegible]						Regress	
	7.4		2100	43	44	2.4	78	11.1	57	47	5.7	0.8	23*	260								
	13**		3098	46	48	3.0	74	16.2	69	84	7.4	0.8	33	860								

* page 70

Patient number Delivery Apgar score	Age days	gest. age weeks	Weight gram	length cm	R $\frac{cmH_2O}{l/s}$	C $\frac{ml}{cmH_2O}$	V_{TG} ml	V_T ml	max $\dot{V}_{in}$ ml/s	max $\dot{V}_{ex}$ ml/	max P_{in} cmH_2O	max P_{ex} cmH_2O	f min	$\dot{V}_E$ ml/min	F_IO_2 %	Dur O_2 days	pH	pCO_2 mmHg	pO_2 mmHg	Comments	X-ray	Diagnosis
16	0.6	32	1520	43	30	2.0		5.7	53	[illegible]	6.2	1.1	86	480	50/40	4.0	7.23	72	59		Ret gran.?	IRDS?
Diabetes	6		1500	43	16	3.8	70	6.0	40	38	2.0	0.7	93	560								
mellitus	13**		1520	44	40	2.3	77	10.4	50	34	5.9	1.3	51	530								
(Apg. 3)	34		1940	47	29	2.0	151	14.7	60	116	8.3	1.1	54	790								
17	0.1	35	1780	43	61	1.0	40	5.8	43	37	6.3	2.7	77	440	36/36	4.7		a54	77		Ret gran.?	IRDS?
Toxicosis	2.0		1800	43	35	2.3		7.8	36	33	4.3	0.5	78	610	28		7.36	a28	65			
levis	6		1670	43	30	3.2		9.2	23	16	3.1	0.8	36	330								
(Apg. 4)																						
18	0.9*	33	2120	46	198	0.59		5.8	48	39	11.0	4.6	71	410	40/40	4.4	7.23	v48			Ret gran.?	IRDS
Duplex	1.8		2170	46	52	0.77		6.1	59	41	8.8	1.2	108	660	40		7.30	v48				
	2.8		2090	46	93	0.63		4.8	38	29	7.3	1.1	92	440	40		7.30	v54				
	5.8		1930	46	58	2.5	37	8.0	28	20	4.0	1.0	46	370	28							
(Apg. 9)	21		2090	46.5	38	3.0		12.3	54	38	5.2	0.9	57	690								
	30		2340	46.5	102	3.7		16.9	53	39	7.6	1.7	42	710								
19	1.0*	39	3720	52	63	2.6		16.4	70	68	9.2	2.9	72	1180	30/30	2					Aspir PL	Aspir syndr
Normal	6**		3460	52	51	4.1	48	17.1	72	63	6.5	1.8	67	1140								
(Apg. 8)																						
20	0.5	37	2950	49	47	1.5	53	11.2	63	60	8.3	1.5	68	990	30/30	1	7.31	v45			Aspir	Aspir syndr
(Apg. 5)																						
21	0.3	43	3960	53	20	4.1	141	11.6	83	84	2.7	1.0	115	1330	26/26	2.8		a42			{Aspir PL	Aspir syndr.
Normal	1.6		3800	53	45	2.4		11.5	80	84	6.2	1.9	109	1270	24						Regress	
	2.4		3670	53	33	4.5		16.4	102	93	3.4	3.2	91	1490	[illegible]							
(Apg. 9)	5**		3800	53	33	6.0		15.8	60	56	3.7	1.0	63	990							0	
22	0.3	36	2850	50	77	1.2	118	9.7	85	61	9.2	3.8	74	720	26/26	1	7.28	v45			Aspir	Aspir. syndr.
Normal	1.3		2600	50	33	3.5	142	10.7	93	37	4.5	1.0	68	640							{Aspir PM	
(Apg. 10)	2.2*		2700	50	41	3.1	39	11.2	[illegible]	35	4.6	1.2	[illegible]	650							0	
23	1.0*	40	4120	52	34	2.4	98	16.8	146	122	8.3	[illegible]	121	[illegible]	30/30	2.3	7.26	a36			{Aspir PL	Aspir. syndr
Normal	2.7		4130	52	56	4.5		22.6	91	76	6.1	4.6	97	2160							0	
(Apg. 8)																						
24 Sudden delivery (Apg. 9)	0.3	40	3840	[illegible]	79	1.6	48	12.8	77	89	9.6	3.2	95	1210	30/30	2	7.26	v42			Aspir.	Aspir syndr.
25	1.0*	[illegible]	5140	56	29	2.0		12.6	135	112	7.7	1.3	135	1700	21/21	0					{Aspir PL	Aspir syndr
Normal	2.0		5060	56	37	4.8	67	14.0	129	97	4.1	3.1	112	1560								
	4.2		5040	56	38	3.5		16.2	114	97	3.6	3.8	102	1680								
(Apg. 9)	10*		[illegible]870	56	49	4.0		22.7	[illegible]	54	7.0	2.6	59	1340								

26	1.0	37	3450	32	39	3.7	34	12.2	42	38	3.5	0.9	45	550	30/30	2.0	7.37	a43	85	Asph.	Asph. sympt.
	1		3290	33	86	3.9	55	14.5	36	36	3.8	2.0	36	330	28		7.37	a39	86		
Series	1.9*		3290	33	60	3.1		13.0	33	28	3.3	1.4	48	630	26						
(App. 5)	7.0**		2940	32	34	5.7		14.5	47	34	3.7	0.8	41	600							
27	0.5**	40	3350	58	23	2.6	10	14.0	87	96	6.1	1.0	97	1360	28/28	[illegible]	7.31	b38		Asph. PL. 0	Asph. sympt.
Normal	2.1		3140	58	33	3.5	82	11.7	78	82	5.2	1.9	114	1350							
(App. 8)	6		3250	58	116	8.7		10.3	58	44	0.7	3.3	44	800							
28	0.5	40	3330	50	20	2.7	39	9.2	68	54	3.7	0.9	108	990	30/30	2	7.35	a37	59	Asph.	Asph. sympt.
Normal	6**		3290	50	28	4.7	131	13.6	103	79	4.5	1.2	87	1190							
(App. 10)																					
29	1.3	32	1700	41	49	1.6	88	8.4	15	31	3.6	0.6	55	300	34/30	7	7.38	a38	60	Asph. 0	Asph. sympt.
Normal	4.1		1720	41	36	3.2		10.5	36	41	3.8	0.8	60	630	30		7.35	a35	98		
	17**		1770	42	39	2.9		11.5	43	42	4.9	1.1	65	740							
(App. 9)	40		2360	46	47	1.3	55	11.2	63	60	8.3	1.5	88	980							
30	1.2*	34	3100	49	32	3.8	83	12.7	61	54	3.2	1.6	70	890	30/28	2	7.40	37		Dissemin. atelectasis	?
Normal	2.1		2990	49	37	4.7	85	14.4	66	62	4.0	1.9	70	1080							
(App. 10)																					
31 Intra-uterine asphyxia+VE (App. 5)	1.3	25	2600	48	88	2.7	36	12.8	58	46	9.9	3.3	61	760	30/45	4	7.37	a37	62	Diffuse infiltrates	?
	3.2		2450	48	30	2.6		11.1	63	49	4.9	1.1	73	810	30			a45	88		
32 Sectio Diabetes matris (App. 9)	0.3	39	3320	32	33	3.0	141	13.2	64	45	3.9	3.4	58	[illegible]	38/30	2.0	7.36	a48	92	Dissemin. atelectasis	?
33	1.0*	41	4400	54	37	5.2	104	21.7	77	72	4.8	3.4	61	1330	30/30	2.3	7.39	a42	98	PT PM+ infilt.	?
V.E.	2.0		4360	54	18	6.1	131	22.4	18	79	4.3	0.8	56	1320	24						
(App. 10)																					
34 Normal (App. 8)	1.0*	41	4300	54	71	3.2	101	16.3	93	78	4.3	1.0	83	1370	21/21	0				PT PM +reduced air	?
35 Normal	0.5	38	2940	46	118	2.1		11.7	37	36	[illegible]	3.4	53	650	40/30	1	7.31	b39		Opaque basal area	
(App. 9)	5		2670	46	69	4.1	52	17.4	38	43	6.5	1.3	51	880							
36	1.0	41	3800	51	12	3.9	113	21.3	96	100	8.7	0.8	88	1850	40/24	1	7.33	b34		PM small infiltr.	?
	2.0*		3730	51	29	2.4	128	17.3	83	[illegible]	8.0	2.2	79	1340							
(App. 9)	9		3690	53	33	5.6		25.2	78	53	7.3	[illegible]	46	1130							

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Notes.

Patient cathegories	*Patient number*
IRDS	1–18
Aspiration syndrome	19–29
Unclassified disorders	30–36
Low C	1–25 35–36
Normal C	26–34
High R	3 5 9 12, 18 22 24 25 31 35
Normal R	1 2, 4 6–8 10, 11 13–17 19–21 23 26–30, 32–34 36

Column Age: denotes observation made at or near the peak of the disease, representing the infant during disease in section III–V

denotes recovery observation, defined in text.

Column f denotes value calculated from graphs.

Column F_iO_2. At the first observation in every infant th *maximal* oxygen concentration given during the disease denoted together with the oxygen concentration in i spired air during the first observation.

Column P_{CO_2}. a in arterial blood, venous blood and k capillary blood

Column X-ray Abbreviations used

Ret.gran.	reticulogranular pattern
PT	pneumothorax (small)
PM	pneumomediastinum
PL	pleural liquid
0	not pathological

List of Supplements to Acta Paediatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksell Tryckeri AB, Uppsala, Sweden without charge.)

181. Koch, Günther, Lung Function and Acid-Base Balance in the Newborn Infant. 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. 1968
185. Andersen, Eva, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. 1968
186. *Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases.* 1968
187. Karlberg, Petter *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. 1968
188. Mossberg, Gunnar W., and Malis, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. 1969
189. Fällström, S. P. On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. 1969
190. Heymann, P. Yngve, Experimental Studies on Closure of the *Ductus Arteriosus Utilizing Whole-Body Freezing.* 1969
191. Kaijser, Anti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kumento, Astrid, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. 1969
195. Thore, Ingrid, Cerebral Symptoms in the Newborn. 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. 1969
197. Sandin, Elov, *Pseudomonas Infections in a Paediatric Surgical Unit.* 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. 1969
199. Villmöld, Ebba, Tape Recordings of the Electrocardiogram in Newborn Infants. 1969
200. Bayer, Olga M., Corvisier, Jacquin, Roman, Lydia and van Veen, Astrid, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. 1970
201. Bartholomew, Lynette E., Hartwell, Phyllis, Bolls, John U., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. 1970
202. Fomon, Samuel J., Filer Jr., L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. 1970
204. Berg, Kristina, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. 1970
205. Zweymüller, Ernst and Preining, Othmar, *The Insensible Water Loss of the Newborn Infant.* 1970
206. *Proceedings of the Thirteenth Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Mauri Dahl. 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Childpsychiatric and Electroencephalographic Study on Primary School Children in Umeå. 1970
210. Rosberg, Georg, Parental Attitudes in Pediatric Hospital Admissions. 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. 1971
212. Haludkas, Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. 1971
214. Samuelson, Gösta, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. 1971
215. Bergsten, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped Children. 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Inf…
217. *Pediatric Work Physiology. Proceedings of the Third International Symposium, Stockholm, August 30–September…* Edited by Claes Thorén. 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. 1…
219. Jaffé, Doris, Hartmann, Stanley, Manning, Mary and …ckle, Coronary Arteries in Newborn Children. In… tions in Longitudinal Sections and Their Relationshi… and Experimental Data. 1971
220. *Holkama, Niilo, Bäckström, Leena, Kantero, Ritva-L…* *sala, Ritva, Studies on Growth of Finnish Childre…* to Ten Years. 1971
221. Bohman, Michael, A Comparative Study of Adopt… Foster Children and Children in Their Biological … Born after Undesired Pregnancies. 1971
222. Jukarainen, Erkki, Plasma Magnesium Levels duri… Five Days of Life. 1971
223. Fomon, Samuel J., Thomas, Lora N., Filer, Jr., L… Ekhard E., and Leonard-Mitchell T., Food Cons… Growth of Normal Infants Fed Milk-based Form…
224. Kleckenberg, Gunnar, *A Prospective Longitudina…* Children. Data on Psychic Health and Developm… Years of Age. 1971
225. Sundström, Folke, Physical Growth of Children wit… Heart Disease. Pre- and Postoperative Study of … 1971
226. Hagberg, Bengt, Sanner, Gunnar, and Steen, Mark… equilibrium Syndrome in Cerebral Palsy. Clinical A… Treatment. 1972
227. Anttila, Ritva, Renal Involvement in Juvenile R… Arthritis. A Clinical and Histopathological Study. H…
228. Hellström, Ferdl, Westerlin, Hallsti, Ekblom, Gun… Sten, Mårtin, *Chronic Respiratory Paralysis. A Clini…* 12 Patients in Long-term Respirator Treatment aft… tis. 1972
229. Bucci, Giovanni, Scalamandrè, Antonio, Savignoni, P… Mendicini, Modesto, Picece-Bucci, Silvana, and wi… collaboration of Marinosa, Leonardo, The Systemic Sy… Pressure of Newborns with Low Weight. A Multiple… Analysis. 1972
230. Annerholm, Ebba, Late Prognosis of Children Born … culous Households. The Effect of Isolation and B… BCG-vaccination. 1972
231. Stenslund Junker, Karin, Selective Attention in Infan… Imitative Communicative Behavior. 1972
232. Hagne, Ingrid, Development of the EEG in Normal I… ing the First Year of Life. A Longitudinal Study. 19…
233. Wartiainen, Heikki, Microangiography of the Liver. … mental Study of Sheep from the Prenatal to the … Period. 1972
234. Gerrard, J. W., MacKenzie, J. W. A., Goluboff, N., G… and Maningas, C. S., Cow's Milk Allergy: Prevalence… festations in an Unselected Series of Newborns. 1973
235. Köhler, Lennart, Health Control of Four-Year-Old C… Epidemiological Study of Child Health. 1973
236. *Proceedings of the Fourteenth Nordic Paediatric Con…* Gjövik, June 27–June 30, 1973. Edited by Peter Johan…
237. Sillanpää, Matti, Medico-Social Prognosis of Children… lepsy. Epidemiological Study and Analysis of 245 Pat…
238. Strom, Jürgen, von Willebrand's Disease in Sweden. 1…
239. Harris, Pertha, The Finnish Stork Legs Children… Psychiatric Study. 1973
240. *Rearing of Non-identical Twins with Lymphopenic Hy…* *globulinaemia under Gnotobiotic Conditions. Edited…* Fuller. 1973
241. Soland, Toivo T., Haptoglobin Levels in the Plasma of… Infants, with Special Reference to Infections. 1973
242. Valkeakari, Tapio, *Analysis of Serial Echoencephal…* Healthy Newborn Infants During the First Week of Li… parative Study by One- and Two-dimensional Echo… graphy. 1973
243. Lundström, Nils-Rune, Clinical applications of echocar… in infants and children. 1974
244. Ahlström, Hans, Studies on Pulmonary Mechanics i… 1974
245. Iversen, Ulla, Hereditary Nephropathy with Hea… "Alport's Syndrome". 1974
246. Omar, Jakob, Training of Medical and Dental Studen… tal Retardation. 1974
247. Hjalmarson, Ola, *Mechanics of Breathing in Newbor…* with Pulmonary Disease. 1974

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ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 248 1974

STUDIES ON EARLY NEONATAL HYPOCALCEMIA

BY LARS BERGMAN

ALMQVIST & WIKSELL PERIODICAL COMPANY

ACTA PÆDIATRICA SCANDINAVICA

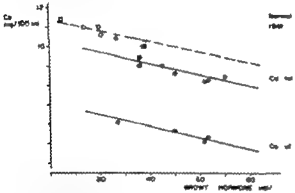
ERRATA

The following lines should read

p 10 left column, line 4 from the bottom: Ca-tot (Table 1 and Fig. 2) was significantly high-

p 18 left column, line 27 glycemia and hypoglycemia (14 16, 30 57).

p 19 left column. Fig. 9 should be replaced by the following figure.



p 19 right column, line 15· "As seen . group" should be deleted.

p. 21 right column, line 29· the secretion of GH (14 16 30, 57). In the present

GÖTEBORG 1974

Göteborgs Offsettryckeri AB, Kungälv 1974

CONTENTS

This summary is based on the studies reported in the following papers.

I. Plasma calcium fractions in normal subjects from birth to adult ages, L. Bergman & B. Isaksson. *Acta Pædiat Scand* 60:630-636 1971

II. Plasma calcium fractions during the first days of life with special reference to Neonatal hypocalcemia, L. Bergman. *Biol Neonate* 20:346-359 1972.

III. Calcitonin and parathyroide hormone – relation to early neonatal hypocalcemia in infants of diabetic mothers, L. Bergman, I. Kjellmer & U. Selstam. *Biol Neonate* (Accepted for publication).

and from the following unpublished studies:

IV. Relations at birth between mother and infant and between vaginal delivery and caesarean section in total and ultrafiltrable calcium, phosphorus and total proteins.

V. Growth hormone during the first day of life in infants of diabetic mothers and normal infants and its relation to plasma calcium.

INTRODUCTION

Tetany in the neonatal period was first described by Kehrer 1913 (34). At that time no biochemical investigations were carried out but it was indicated that these patients had an excellent therapeutic response to the oral administration of calcium chloride. In 1917 Howland and Marlott (29) reported the first satisfactory chemical study and there was a vague understanding of the relation between tetany and hypocalcemia.

Infants showing signs of hypocalcemic tetany within a few hours of life were reported by Shannon 1923 (47), Bakwin 1937 (8) and Willi 1939 (58).

Early neonatal hypocalcemia (NHC) is clearly distinguished from the well established later form of neonatal hypocalcemia which usually occurs at the end of the first week of life (53). This later form of hypocalcemia has been shown by Gardner et al. (22) to be induced by a phosphate load when the infant is fed too much with cow's milk. As this late form is well documented the interest of the present study has been focused on the more obscure early form of neonatal hypocalcemia.

The symptoms of NHC vary in the literature but the most commonly noted signs of NHC are »jitteriness» or hyperactivity, twitching of one or more of the extremities and changes in muscle tone. Early NHC should be considered to be present when these signs occur during the first 36 hours of life together with a low plasma calcium. The signs should also subside when the plasma calcium is normalized.

Several studies on early neonatal NHC also called »first-day NHC», »NHC in the first 36 hours of life» have been done (2, 11, 12, 17, 20, 23, 25, 28, 33, 35, 37, 40, 42, 44-46, 52, 53, 59).

These studies have established that NHC occurs more often in pre-term infants and in infants of diabetic mothers (IDM) than in normal infants (17, 25, 52, 53, 59). The incidence of NHC varies from 26 to 50 % in pre term infants (12, 25, 53) in contrast to 1.2 % in full-term infants (12, 17, 25). Zetterström and Arnhold (59) described NHC in 9 of 19 IDM (50 %) while Gittleman et al. (25) reported 27 % when insulin-dependent diabetic mothers and 20 % when »prediabetic» mothers. Tsang et al. (52) found an incidence of NHC of 25 %. This increased incidence was largely related to the incidence in White's class B, C and D. The authors found this incidence of NHC to be significantly increased even when gestational age and perinatal complications were taken into consideration (52).

Some authors have found a higher incidence in connection with caesarean section and after complicated deliveries (17, 25, 46, 59), while others have not (52, 53).

Different values have, however, been reported for total plasma calcium (Ca-tot) at which early NHC occurs. The values range from 7-9 mg/100 ml plasma (12, 28, 46, 53, 59). 7 mg/100 ml plasma is most commonly accepted as the limit (53). Many authors have, however, reported several cases in whom no clear-cut correlation existed between the value of total plasma calcium and the clinical signs of NHC (12, 17, 35, 45).

Bruch and Weintraube (12) found that even with levels of Ca-tot between 6-7 mg/100 ml abnormal signs were noted in only 7 out of 22 observations. Rosenkrantz (45) observed infants with low values of Ca-tot but no signs of NHC. Other authors (17, 50) have noted the same discrepancy between Ca-tot and clinical signs of NHC. With the use of direct measurement of ionized calcium the literature also presents different limits at which NHC appears. Riegel and Harms (42) and Radde (40) give 2.8 mg/100 ml and Brown et al. (11) give 3.5 mg/100 ml as the limit.

Electrocardiogram as a tool in diagnosing NHC has been reported in the literature to be difficult and uncertain especially in newborn infants (23 44).

Concerning the etiology to early NHC there are many different possibilities presented in the literature

1 Hypofunction of the parathyroid glands in the newborn (17 45 52).
2. Increased concentration of plasma phosphorus (12 50, 57 59).
3 End organ unresponsiveness to parathyroid hormone (8 11 15).
4 Steroids from the mother (25 46).
5 An increase in the arterial pH of the infant after birth (35).

The literature presents, however neither an exact mechanism for early NHC nor any certain explanation as to why IDM develop NHC more often than normals.

The purpose of the present studies have therefore been to find answers to the following points.

1 What is the etiology of early NHC?
2. Why do IDM more often develope NHC than normals?
3 Is there any reliable biochemical tool for the diagnosis of NHC?

MATERIAL AND METHODS

The material consists of newborn infants from the Department of Obstetrics, Sahlgrens Hospital, Göteborg. The infants can be divided into four groups:

1 Normal infants delivered vaginally (Paper III n=9 Paper IV n=17 Paper V n=4).
2. Normal infants delivered by caesarean section (Paper II n=10 Paper IV n=8).
3 Infants with clinical signs of early NHC (Paper II n=4).
4 Infants of diabetic mothers (IDM) (Paper III n=11).

Fig. 1 shows the gestational age and birth weight of all infants studied. The material is described in detail in each paper

The analytical methods used were the following Ultrafiltrable calcium (Ca-uf) in plasma was determined according to Bergman and Isaksson (Paper I). Total plasma calcium (Ca-tot) and calcium in the ultrafiltrate were determined by flame photometry (Eppendorf), calcium in the urine was determined by EDTA titration, phosphorus in plasma and urine by the method of Fiske-Subbarow and total proteins by the Biuret reaction.

The method for determination of *Ca-uf* is described in detail in Paper I. Only some points of general interest will be mentioned here

Ca-uf consists of both ionized and complexed calcium. Since complexed calcium is only a small

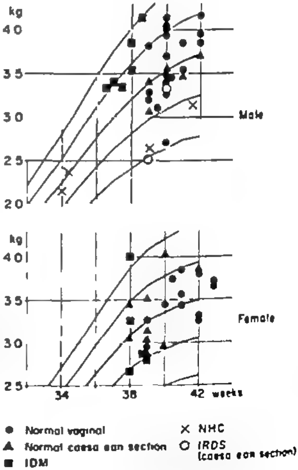


Fig. 1 Birth weight v gestational age (± 2 SD) of all infant studied. (Diagram kindly permitted by Engström, L., Karlberg, P & Selstam, U 1974).

part (14 % of Ca-tot) Ca-uf therefore consists mostly of ionized calcium.

The method is based on ultrafiltration through a collodion membrane under pressure with simultaneous pH and temperature controls. 1.0-2.0 ml plasma is needed and the ultrafiltration procedure takes 10-15 minutes. The determination of Ca-uf was made on the basis of the formula.

$$\text{Ca-uf} = \frac{\text{Ca-f} \times \text{K-p}}{\text{K f}}$$

in which Ca-uf = ultrafiltrable calcium in mg/100 ml plasma, Ca-f = calcium in mg/100 ml ultrafiltrate K f = potassium in mmol/l ultrafiltrate and K-p = potassium in mmol/l plasma.

The method presupposes that the Ca/K ratio in the ultrafiltrate is equal to the ratio between ultrafiltrable calcium in plasma and plasma potassium. The prerequisite for using this formula is that no part of the plasma potassium is bound to plasma proteins. Our results (Paper I) are in agreement with the view that all plasma potassium is ultrafiltrable (K-f = 0.96 x K-p + 0.11). Moreover if a part of the plasma potassium were protein bound our calculation procedure should give erroneously high values for Ca-uf Our values, however agree with those given in recent reports (Robertson et al. 1968 (43) ultrafiltration, Bold 1969 (10) dialysis and Pedersen 1969 (38) ultrafiltration). None of these have used the formula presented in this method.

The advantages of this method when compared with previous methods are that no consideration has to be taken to corrections either for plasma protein volume or for the Donnan effect as the calculation is based on a ratio between the two components in the ultrafiltrate (Ca/K). Moreover no consideration has to be taken to possible dilution or evaporation nor to inaccurate dilution of the ultrafiltrate for the flame photometric determination.

The importance of pH in the determination of Ca-uf is shown by the dissociation curve presented in Paper I. This curve shows that pH has its greatest effect on the distribution of plasma calcium within the pH range compatible with life.

Using this curve the determined value of Ca-uf can be recalculated to the actual value at the moment of blood sampling knowing the actual pH. The exact course of the calcium fractions in the newborn infants after birth can thereby be studied.

Growth hormone (GH) was determined by radioimmunoassay performed with double antibody technique using human growth hormone as well as antiserum against human growth hormone supplied by AB Kabi, Stockholm, Sweden, and the antigen was labelled with J^{125} by the chloramin-T method

Standard was obtained from the Medical Research Council (London).

The determinations of GH were done at the Department of Clinical Chemistry University of Göteborg.

Calcitonin (CT) was determined by radioimmunoassay using J^{125} labelled human syntetic calcitonin supplied by CIBA (Switzerland) by the chloramin-T method and rabbit anti-human antibody

Purification of tracer was achieved by gel filtration. Face separation was done by means of the dextran-coated charcoal method. Human syntetic calcitonin (CIBA) was used as standard. For further details se Almqvist et al. (3).

Parathyroid hormone (PTH) was determined by radioimmunoassay using J^{125} labelled bovine parathyroid hormone supplied by Wilson, Chicago (US) and guinea-pig anti-bovine antibody crossreacting with human parathyroid hormone

Purification of tracer was achieved by gel filtration. Face separation was done by means of the dextran-coated charcoal method.

Bovine parathyroid hormone (Wilson) was used as standard. For further details see Almqvist et al. (4).

CT and PTH were determined at the Immunological laboratories AB in Stockholm.

Standard linear regression analysis were used The significance tests were analysed according to t-test.

When comparison of two mean values the Student's t test was used.

The calculations were done by computer (Olivetti).

RESULTS

A. Total and ultrafiltrable calcium, phosphorus and total proteins. Relations at birth between mother and infant and between vaginal delivery and caesarean section.

A higher incidence of NHC in connection with caesarean section has been found by some authors (17 25 46 59) while others have not (52, 53). Because of these different opinions an investigation was designed to study:

1. The difference between mother and infant at birth in total calcium (Ca tot) and ultrafiltrable (Ca-uf) calcium, phosphorus and total proteins in plasma.
2. If there exists any differences in these parameters when vaginal deliveries are compared with caesarean section.

The material consists of 17 infants delivered vaginally and 8 infants by elective caesarean section and their mothers.

All infants delivered vaginally were full-term and normal. Of the 17 infants one was a breech presentation and one was delivered by an outlet vacuum extractor. None of these two infants suffered from asphyxia.

Of the 8 infants delivered by caesarean section 6 had an uneventful course, one infant developed IRDS and one infant had a short period of asphyxia after birth (Apgar score 5/1 min. and 10/3 min.). The infant who developed IRDS left the hospital in good condition as did the other infants studied.

The indication for caesarean section was: cephalopelvic disproportion (7 cases) and elderly primipara (1 case).

The birth weight of the infants ranged from 2.700 gm to 4 170 gm (vaginal delivery) and from 2.850 gm to 3 860 gm (caesarean section). The gestational age ranged from 39 to 43 weeks and from 39 to 42 weeks, respectively all appropriate for date i.e. within ± 2 SD of birth weight to gestational age (Fig. 1).

All pregnancies were uneventful. Blood samples were taken without stasis from the mother from the cubital vein 10-20 minutes before delivery and from the infants at birth from the umbilical vein.

Calcium

Ca-tot and Ca-uf were significantly higher in the infant than in the mother at birth for both vaginal deliveries and caesarean section, as seen in Table I and Fig. 2. Table I also shows that significant correlations were found between mother and infant for Ca-tot and Ca-uf for both vaginal deliveries and caesarean section. Ca-tot and Ca-uf were significantly lower in both mother and infant when caesarean section were compared with vaginal deliveries (Table II).

Phosphorus

Phosphorus was significantly higher in the infant than in the mother at birth for both vaginal deliveries and caesarean section (Table I and Fig. 2).

Fig. — The difference between mother and infant at birth in Ca-tot, Ca-uf phosphorus and total proteins. (All values of Ca-uf are corrected t pH 7.4).

Table I. *Differences and correlations between mother and infant at birth in Ca-tot Ca-uf phosphorus and total proteins.*

Mean value and standard deviation in parenthesis, are given.

	VAGINAL (n = 17)						CÆSAREAN SECTION (n = 8)					
	Mother	Infant	Difference Infant-Mother		Correlation Infant/Mother r	signif.	Mother	Infant	Difference Infant-Mother		Correlation Infant/Mother r	signif
Ca-tot mg/100 ml	10.4 (0.60)	11.7 (0.97)	1.3	+++	0.876	+++	9.3 (0.46)	10.9 (0.61)	1.6	+++	0.709	+
Ca-uf mg/100 ml	5.9 (0.51)	8.0 (0.82)	2.1	+++	0.634	++	5.4 (0.40)	7.1 (0.51)	1.7	+++	0.758	+
Phosphorus mg/100 ml	2.6 (0.68)	5.5 (0.98)	2.9	+++	0.695	++	3.1 (0.77)	5.5 (0.75)	2.4	+++	0.779	+
Total proteins gm/100 ml	7.3 (0.56)	5.9 (0.57)	1.4	+++	0.414	N.S.	7.0 (0.57)	5.6 (0.41)	1.4	+++	0.320	N.S.

$2p<0.001$ = +++ $2p<0.01$ = ++ $2p<0.05$ = + Not significant = N.S. number = n
correlation coefficient = r

A significant correlation was found between mother and infant for both vaginal deliveries and caesarean section for phosphorus (Table I). No significant differences were found between the mothers or between the infants in the concentration of phosphorus when the two different deliveries were compared (Table II).

Total proteins

The concentrations of total proteins were significantly lower in the infant than in the mother at birth for both vaginal deliveries and caesarean section (Table I and Fig. 2). No correlation was found between mother and infant in total proteins in any of the two different deliveries (Table I). No significant differences were found between the mothers or between the infants in the concentrations of total proteins when the two different deliveries were compared (Table II).

No correlations were found between gestational age and Ca-tot, Ca-uf phosphorus or total proteins, neither between phosphorus and Ca-tot or Ca-uf

Table II *Differences between vaginal delivery and caesarean section.*

	Mother vagin./Mother section		Infant vagin./Infant section	
	$\bar{m} - \bar{m}$	significance	$\bar{m} - \bar{m}$	significance
Ca tot mg/100ml	1.1	+++	0.8	+
Ca-uf mg/100ml	0.5	+	0.9	++
Phosphorus mg/100ml	-0.5	N.S.	0	N.S.
Total proteins gm/100ml	0.3	N.S.	0.3	N.S.

$2p<0.001$ = +++ $2p<0.01$ = ++ $2p<0.05$ = + not significant = N.S. mean value = $\bar{m}$

and furthermore no correlations were found between total proteins and Ca-tot or Ca-uf.

DISCUSSION

The two groups are well matched according to gestational age and birth weight (Fig. 1). All infants delivered vaginally were normal. Two infants delivered by caesarean section developed signs of respiratory difficulties.

Blood samples from the infant at birth were taken from the umbilical vein. Thalme (49) found no differences between umbilical artery and vein in Ca-tot, phosphorus or total proteins.

All values of Ca-uf were corrected to pH 7.4. This correction renders comparisons of mother to infant, mother to mother and infant to infant more correct, as sudden changes in pH give markedly different values for Ca-uf (see Paper I). For total calcium a sudden change in pH is of no importance (40).

er in the infant than in the mother in both groups. This is in agreement with previous findings (6, 19, 31, 51). Also *Ca-uf* (Table I and Fig.) was found to be significantly higher in the infant than in the mother in both groups. This was also shown by Deliyoria-Papadopoulos (19) but Andersh (6), on the other hand, found no difference between mother and infant. As Ca-uf mostly consists of ionized calcium this fraction is also higher in the infant than in the mother, which is in agreement with the findings of Radde et al. (39) and Thalme (51).

Significant correlations between mother and infant for Ca-tot and Ca-uf (Table I) were found in this study for both vaginal delivery and caesarean section. Khattab and Forfar (31) found the same for Ca-tot in vaginal deliveries. Thalme (51), on the contrary, did not find such a correlation for either vaginal deliveries or caesarean section.

The significantly higher levels of Ca-tot and Ca-uf in the infants compared to their mothers in both groups found in this study support previous suggestions of an active transport of calcium over the placenta (19, 56).

The significantly higher values found in this study for Ca-tot and Ca-uf in the mothers when vaginal delivery was compared with caesarean section

might depend on the fact that they were not in a fasting state. All mothers who delivered vaginally had an oral intake of calcium through milk foods. As a significant correlation exists between mother and infant in both Ca-tot and Ca-uf at birth also the infants delivered vaginally had significantly higher values for Ca-tot and Ca-uf than infants delivered by caesarean section.

The concentration of *phosphorus* in this study was significantly higher in the infant than in the mother in both groups probably due to an active transport of phosphorus from the mother to the infant. This is in agreement with previous studies (31 51).

The significantly lower concentration of *total proteins* in the infant than in the mother found in both groups depends on the infants low capacity for producing proteins. As there was no significant difference in the gestational age between the two groups no significant differences between the infants in the two groups were found in total proteins.

B Total calcium, Ca-fractions, phosphorus and total proteins during the first days of life

To study the development of the course of calcium, phosphorus and total proteins in plasma after birth blood samples were taken at different intervals between 1 24 h of life for determinations of Ca-tot, Ca-fractions, phosphorus and total proteins in ten infants delivered by elective caesarean section (Paper II).

The measured values of Ca-uf were corrected to the actual pH of the infant at the moment of blood sampling and thereby represent the actual values of Ca-uf. Urine for determination of calcium and phosphorus was collected between the blood samples.

All infants were full-term. Five infants were normal three infants developed signs of respiratory difficulties (2 IRDS and 1 because of aspiration), one was dysmature and one was depressed at birth by anesthetics. The birth weight ranged from 2.500 gm to 4 040 gm and the gestational age from 38 to 42 weeks (Fig. 1) (For further details and clinical data of mothers and infants see Paper II).

Ca-tot decreased after birth in all infants studied. Minimum values were reached after 20 h of life. The mean decrease was 2.1 mg/100 ml plasma.

Also *Ca-uf* decreased after birth and the decrease was more marked during the first 6 h of life with a mean decrease of 0.7 mg/100 ml plasma. The lowest values were reached after [illegible] h of life. The mean decrease was 1.5 mg/100 ml plasma. Three infants with no clinical signs of NHC had Ca-uf values as low as 5.2 5 5 mg/100 ml plasma at 24-29 h of life. Two of these infants developed IRDS and the third infant was the only infant who lost calcium in the urine

Two different groups of infants were found one starting with lower values for Ca-uf than the other (95 % level, tested by the Mann-Whitney U-test). The difference remained during the time studied as judged from values measured for the time intervals. 1 3 h, 4-8 h and 21 36 h after birth.

Up to 12 h of life there was no particular change in the *protein-bound Ca-fraction Ca-prot* (Ca-tot minus Ca-uf) while after that a decrease was seen. The lowest values were found after 20 h of age.

The concentration of *phosphorus* varied with pH changes up to 1[illegible] h of life. When an acidosis developed the concentration of phosphorus increased and when the acidosis was corrected the concentration of phosphorus decreased. After 12 h of age however a tendency towards an increase in the phosphorus concentration was seen.

No particular trend in the levels of *total proteins* was found.

The concentration of *calcium and phosphorus in the urine* were negligible during the first 48 h of life The only exception was one infant who lost 12 mg calcium in the urine. This infant was one of the three infants who reached the lowest values of Ca-uf after birth.

Early neonatal hypocalcemia (NHC)

In order to clarify if Ca-uf correlates better with the clinical signs of NHC than does the Ca-tot, four infants with signs of NHC were studied (Paper II).

Two infants were pre term. One of these developed signs of respiratory difficulty and was treated with i.v. glucose-bicarbonate the other one was a twin and immature. Two were full-term. One of these developed signs of respiratory difficulty and was treated with i.v. glucose-bicarbonate- the other one was mildly depressed at birth and was vomiting. All the four infants had received minimal amounts of calcium (5 4-10.8 mg) up to the time when the signs of NHC started.

When the value of Ca-uf in these infants decreased to or below 5 0 mg/100 ml plasma, clinical signs of NHC were noted. After treatment with calcium-gluconate orally (Calcium-Sandoz) the value of Ca-uf increased above 5 0 mg/100 ml and the signs of NHC subsided. No such correlation between the signs of NHC and total plasma calcium was found. Two of the infants had Ca-tot values above the commonly accepted limit 7 0 mg/100 ml and one of them even above 8.0 mg/100 ml at the time they had signs of NHC.

DISCUSSION

The decrease in the concentration of plasma calcium that develops during the first days of life is also called the ›physiological hypocalcemia‹ (21) Its etiology has been discussed in the literature but the most commonly accepted theory is that the infant, after birth, is deprived of the calcium transport across the placenta at a time when too little oral calcium after birth does not meet the demands for calcium from the tissues and the skeleton (21 36 45 53).

This decrease in the calcium concentration is caused primarily by a decrease of the Ca-uf fraction as shown in Fig. 3 (Paper II) and Figs. 3 and 4 Ca-uf decreased most markedly up to 10-12 hours of life while Ca-prot, during the same time showed no particular change. Up to 10-12 hours of age the decrease of Ca-tot is thus mostly caused by a decrease in the Ca-uf fraction.

After 10-12 hours of age and up to 21 36 hours of age a decrease was seen in both Ca-uf and Ca-prot but somewhat more marked in Ca-uf During this period the decrease of Ca-tot is therefore caused by a decrease in both fractions but primarily of the Ca-uf fraction. In the present material two different groups of infants were found one starting with higher values for Ca-uf at birth than the other These higher values also remained significantly higher As seen in Fig. 4 (Paper II) the decrease of Ca-uf is the same in the two groups and the main reason that one of the groups reaches lower values is the lower values for Ca-uf at birth. The Ca-uf level in cord blood might thus be indicative of the risk that the individual infant has in developing NHC.

As the Ca-uf fraction consists mostly of calcium ions on which the irritability of the nerves and muscle cells depends, determination of Ca-uf is a more useful measure of the decrease of calcium ions in plasma than the plasma total calcium concentration. A measure of the concentration of the calcium ions is of great importance when the newborn infant shows signs of NHC.

The decrease of Ca-tot found in this study is more marked than the decrease found by Acharya et al. (2) but somewhat less than the decrease found by Radde et al. (40). Thalme (49) who studied the Ca-tot level during the first 15 minutes after birth found no definite change in the Ca-tot level.

The literature presents different opinions concerning the relation between calcium and phosphorus in plasma after birth a decrease of calcium combined with an increase of phosphorus (8 31 53) or a parallel decrease of both calcium and phosphorus (2) or no special trend during the first 36 h of age (12) and even up to 72 h of age (11) or a decrease of calcium in plasma 24 h after an increase in phosphorus (52). In the present material both decrease and increase in the phosphorus concentration were seen up to 12 h of life even in the same infant. During the same time there was a decrease of calcium. Therefore this period up to 12 h of life provides an exception to the rule that when plasma phosphorus increases plasma calcium decreases. Thereafter a tendency towards an increase in the concentration of phosphorus appeared.

Up to 12 h of age the phosphorus concentration was negatively correlated to the pH of the infant.

This pH dependency of the phosphorus concentration after birth is in agreement with the findings of Thalme (49).

The different values for total plasma calcium at which NHC occurs and the discrepancy between Ca-tot and signs as found in the literature demonstrate that total calcium as a test in the diagnosis of NHC is unreliable. The literature also presents different values for ionized calcium at which NHC appears. Riegel et al. (42) and Raddo (40) give 2.8 mg/100 ml and Brown et al. (11) give 3.5 mg/100 ml as the limit. These values are lower than the values found in this study even when corrected for complex-bound calcium. In the present material, Fig. 1 (Paper II) 2 of the infants with NHC showed total calcium levels above the commonly accepted 7.0 mg/100 ml and 1 of them even above 8.0 mg/100 ml while all 4 had Ca-uf values at or below 5.0 mg/100 ml plasma. Thus this level might be the critical level at or below which signs of NHC may occur.

C. Calcitonin and parathyroid hormone-relation to early neonatal hypocalcemia in infants of diabetic mothers (Paper III)

Radioimmunoassay has now made it possible to estimate parathyroid hormone (PTH) and calcitonin (CT). These two hormones regulate the calcium concentration in plasma. It was therefore of great importance to study these hormones in relation to early NHC. As early NHC occurs more often in infants of diabetic mothers (IDM) these infants were chosen for this study.

Eleven consecutive cases of IDM and 9 healthy term infants were studied. All control infants were delivered vaginally. Of the IDM 7/11 were delivered by caesarean section, 2/11 by vacuum extractor and 2/11 vaginally (for further details see Paper III).

Blood samples were taken in all infants at 24 h (range 21-29) and at 48 h (range 43-54) of age and in cord blood. In most of the IDM a sample was also taken between 1-12 h of age. Urine was collected in the intervals between the blood samples in the IDM. At each blood sample a regular clinical evaluation of the infant was performed according to a protocol with special emphasis on signs of neuromuscular irritability.

Both *Ca-tot and Ca-uf* decreased after birth (Figs. 1 and 2, Paper III). The decrease was more marked in IDM in both Ca-tot and Ca-uf. Minimum values were reached at 24 h of age in both groups. The mean values for Ca-tot at 24 h age were 8.7 ± 0.6 mg/100 ml plasma for the IDM and 9.9 ± 0.2 mg/100 ml for the controls ($p<0.001$). The mean values for Ca-uf at the same time were 5.4 ± 0.4 mg/100 ml and 6.3 ± 0.2 mg/100 ml for the two groups, respectively ($p<0.005$).

After 24 h of age an increase in Ca-tot and Ca-uf was seen in both groups. The difference between the two groups persisted however in both Ca-tot and Ca-uf ($p<0.0?$ and $p<0.05$, respectively). No significant difference was seen in cord blood.

Three infants had signs of increased neuromuscular irritability. These infants had at the same time one or more occasions of Ca-uf values at or below 5.0 mg/100 ml. The mode of delivery was different in all three cases: one vaginal, one by caesarean section and one by vacuum extractor. The gestational age was 39, 38 and 36.5 weeks respectively.

No significant differences in the *phosphorus* concentrations were seen between the two groups at either 24-48 h or in cord blood. The concentration of phosphorus did not increase between cord blood and 24 h of age but a slight increase was observed in the mean values for both groups between 24 and 48 h of age. This increase was however not statistically significant in the IDM. No correlation was seen between the phosphorus values and Ca-tot up to 48 h of age in any of the groups.

No significant differences were seen in the concentrations of *total proteins* between the two groups at either 0, 24 or 48 h of age. No significant correlation was seen between the concentration of total proteins and Ca-tot in any of the groups up to 48 hours of age.

Both IDM and the controls had levels of *calcitonin* (CT) in cord blood within the normal range for adults. After that an increase was seen in bot

groups and maximum values were reached at 24 h of age Up to 48 h of age a decrease was then seen in all cases investigated. No consistent difference was found however between the two groups.

A significant negative correlation ($p<0.01$ $r = -0.61$) was found between Ca tot and the level of CT in IDM both at 24 h and 48 h of age No such correlation was found in the control group

In four IDM and two controls the levels of *parathyroid hormone* (PTH) were determined up to 48 h of age in all infants except one IDM who was only investigated at birth. In three diabetic mothers in whom the values of PTH were determined at delivery all had values within the normal range.

Only one infant had an increase in the concentration of PTH after birth. The others had low values during the time studied. This infant was an IDM who had a dramatic course after birth with clinical signs compatible with early NHC and signs of impared intestinal passage The signs of early NHC appeared together with low plasma calcium and Ca-uf at 5.0 mg/100 ml. Despite the elevated PTH level the plasma calcium did not increase and the signs of early NHC persisted. The only effect of the elevated PTH level that was seen was a phosphaturia (62 mg/24 h) which resulted in a decrease in the concentration of plasma phosphorus.

Calcium and phosphorus in the urine were studied in 10 IDM. The output of calcium was nil in all 10 IDM investigated.

During the first 24 hours of life between nil and 12 mg phosphorus (mean 2.4 mg) were excreted and in the ensuing 24 hours between nil and 62 mg (mean 14 0 mg).

The *blood sugar* values at 24 h of age were significantly lower in the controls than in IDM ($p<0.001$). No significant differences were found in cord blood and at 48 h of age.

II Comparisons between various infants during the first day of life

A comparison between IDM and the two groups of control infants, one delivered vaginally and one by caesarean section in Ca-tot, Ca-uf and pH at the time intervals. 0 1 3 4-8 and 21 36 hours of age

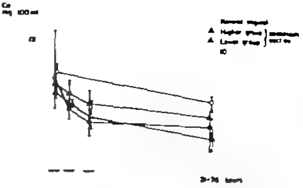


Fig. 3. Total plasma calcium during the first day of life in infants delivered vaginally by caesarean section and in IDM.

is seen in Figs. 3-6. The group of controls delivered by caesarean section was subdivided in two groups, a higher and a lower (Paper II).

Fig. 3 shows *Ca-tot* (mean values and ranges are given). The decrease was more marked in IDM during the first hours after birth. There were no significant differences between IDM and the lower or higher groups. The higher group however tended to decrease somewhat less than the IDM and also than the lower group. All the four groups studied showed the same value for Ca-tot in cord blood. The infants delivered vaginally had significantly higher values than the other groups at 21 36 hours of age

In Fig. 4 the *Ca-uf* is shown. The lower group, as shown in Paper II has significantly lower values for Ca-uf than the higher group and follows very closely the IDM. The higher group on the contrary

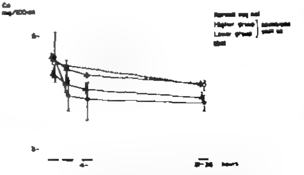


Fig. 4 Ultrafiltrable calcium in plasma during the first day of lif in infants delivered vaginally by caesarean section and in IDM. (All values corrected t the actual pH of the infants at the moment of blood sampling).

follows the vaginally delivered infants who have significantly higher values for Ca-uf than the IDM as shown in Paper III.

The infants delivered vaginally had significantly higher values than IDM and than the lower group at 21 36 hours of age and were significantly higher than the lower group at birth. No significant differences were seen between the higher group and infants delivered vaginally

Table III. *Food carbohydrates, calories and calcium intake up to 24 hours of age.*

Mean values and ranges, in parenthesis, are given.

		n	BM ml/kgBW/24h	G	GF	Calories kcal/kgBW/24h	Calcium mg/kgBW/24h	Ca-tot mg/100ml	Ca-uf mg/100ml	Total proteins gm/100ml	Phosphorus mg/100ml
	IDM	11	45	4	8?	67	13	8 7 (7 4-9 4)	5 4 (4.9 5.8)	5.5 (4.8-6.8)	5.5 (4.8-7.3)
	IRDS	2	6	8	57	30	1.8	7 4	5.5	5 0	7.3 (7.2 7 4)
Caesarean	Lower	2	10	12		12	3	9 0 (8 1-9.8)	5.8 (5 7 5.9)	6.2 (5.5-6.8)	6.1 (4 9-7.3)
section	Higher	2	10	13		12	3	9.2	6 4 (6.3-6 4)	5.8 (5.3-6.2)	6 7 (5 7 7 7)
	Vaginal	9	9	23		16	2 7	9.9 (9 4-10.2)	6.3 (6.0-6.6)	6 1 (5 9-6 7)	5.5 (2.8-7.3)

n = number BM = breast milk G = glucose GF = glucose fructose

Table III shows the food intake (breast milk, glucose, glucose-fructose i.v.) *calories and calcium up to 24 hours of age*. The mean values and ranges for Ca-tot, Ca-uf total proteins and phosphorus at 24 hours of age are also given. The intake of breast milk was higher in the IDM than in all other groups. This was also true for calcium. Only IDM and the infants with IRDS received glucose infusions. The total intake of carbohydrates (glucose plus glucose fructose) was therefore much higher in IDM and the infants with IRDS. This was also true for calories. No significant differences were seen in the concentrations of phosphorus and total proteins between the groups. The mean values for total proteins were somewhat lower and the mean value for phosphorus was somewhat higher in infants with IRDS than the others but the material was too small for any statistical analysis.

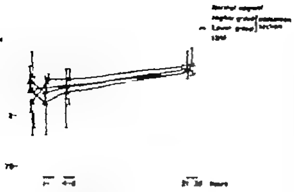


Fig. 5. pH during the first day of lif in infants delivered vaginally by caesarean section and in IDM.

Fig. 5 shows *pH* after birth. Only IDM had a marked increase in pH during the first hours after birth. In both the higher and the lower group a decrease in pH was seen after birth.

After 4-8 hours of age pH increased in both groups and at 21 36 hours of age all groups were very similar

In Fig. 6 those two infants in the lower group who developed *IRDS* are compared with the other two infants in the same group One of these two latter infants was dysmature and had a neonatal hypoglycemia and one was depressed at birth be cause of anesthetics. The material was too small for statistical analysis. No clear-cut differences were seen in Ca-uf Ca-tot was lower at 21-36 hours of age in the infants with IRDS than in the others, otherwise the groups were very similar

Fig. 6. Total and ultrafiltrable calcium in plasma during the first day of life in infants delivered by caesarean section (lower group in which IRDS are shown separately) and in IDM. (All values of Ca-uf are corrected to the actual pH of the infants at the moment of blood sampling).

DISCUSSION

It is clear from the results presented in this study that the decrease in total plasma calcium during the first 24 hours after birth is more marked in IDM than in infants delivered vaginally (Fig. 1, Paper III). The decrease was also more marked in IDM when compared with normal infants delivered by caesarean section (Fig. 3). This is in agreement with Tsang et al (52) Zetterström et al. (59) and Gittleman et al. (24). Thalme et al. (50) on the contrary found that normal infants decreased more than IDM. These normal infants were not fed until 18 hours of age and the total intake of calcium and calories during the first day of life was very small compared with IDM. Because of starvation these infants had an increase in the phosphorus concentration (50).

There appears to be no reports in the literature on post-natal Ca-uf in IDM. In the present study Ca-uf decreased more markedly in IDM than in the controls (Fig. 2, Paper III) and also more than in normal infants delivered by caesarean section (Fig. 4). Thalme (50) who estimated ionized calcium by the formula of Zeisler found after a small decrease immediately after birth no further change in the concentration of ionized calcium and no difference between IDM and normals. This in spite of the fact that both groups had a decrease in Ca-tot and that the normal infants decreased more than did IDM in that series. In the present study Ca-uf was determined. Since Ca-uf, which consists mostly of ionized calcium, decreased in the present study in both IDM and normals after birth, a decrease in ionized calcium seems to appear after birth. This is in agreement with the findings of Radde et al. (40).

In the present study 3 of 11 infants developed signs of NHC (27 %) while none occurred in the control group. This is in agreement with Gittleman et al. who also found 27 % (24) and Tsang (52) who found 25 %. Of these 3 IDM two were born of White s class C diabetic mothers and one of a class A diabetic mother No relation to the mode of delivery was found.

The intake of calcium was much higher in IDM than in the controls in the present study In spite

of this, IDM developed a more marked decrease in both Ca-tot and Ca-uf than the controls. Tsang et al. (52) found that the decrease in Ca-tot was more marked in IDM in spite of the same intake of calcium orally as the controls.

No correlation was found in the present study between the gestational age and the lowest value of Ca-tot after birth, probably because of the small number of infants and the very small range in gestational age. Tsang et al. (52) who had a wider range in gestational age in their material found a significant correlation between the gestational age and the lowest Ca-tot.

The limit for Ca-tot at which the signs of NHC appear in IDM is not well defined in the literature. Many authors have found a discrepancy between the value of Ca-tot and signs of NHC (44 46 50 52) in IDM. In Paper II it was demonstrated that the clinical signs of NHC appear when the values of Ca-uf reach levels at or below 5.0 mg/100 ml plasma. The present findings in IDM corroborate these findings: The three IDM who developed clinical signs of NHC all had values for Ca-uf at or below this level.

An increase in pH after birth up to four hours of age was seen in this study in IDM (Fig. 5). This increase in pH makes the decrease of Ca-uf during the first four hours of age more marked than the decrease of Ca-tot, as more calcium ions are bound to the proteins. As calcium ions therefore can decrease more than Ca-tot and even when the concentration of Ca-tot is nearly unchanged (40) it is not surprising that a discrepancy between clinical signs of NHC and Ca-tot is noted in the literature. This also indicates that estimations of Ca-uf are a better means of diagnosing NHC.

The concentration of phosphorus was of no importance for the decrease of calcium in plasma in this material as no significant change in the concentration of phosphorus was seen during the period studied in IDM and no correlation was found between Ca-tot and phosphorus. An increase in the concentration of phosphorus has been suggested as the cause of the decrease of calcium after birth in IDM (50, 52, 59). In the present study plasma calcium decreased in IDM in spite of no significant increase in the phosphorus concentration which indicates that there may be another main cause to the decrease of plasma calcium in IDM than the phosphorus concentration.

The decrease of blood sugar after birth stimulates the secretion of glucagon (9). Glucagon stimulates the secretion of CT (7). Böttger et al. (13) have shown that glucagon-like-immuno-reactivity (GLI) from the gut can be released when glucose or calcium lactate are given orally GLI also stimulates the secretion of CT (13). The newborn infant has therefore two possible ways of stimulating the secretion of CT During the first hours of age when IDM reach their lowest values of blood sugar the concentration of CT start to increase (Fig. 3 Paper III). This increase which reached its maximum level at 24 hours of age, was also seen in the controls. After 24 hours of age a decrease was seen in both groups. The concentration of CT was very high. Hesch et al. (27) have also found very high levels of CT in newborn infants, above normal adult standards in all infants and in some even up to six times the upper limit of adult standards. David et al. (18) also found that CT was higher in newborn infants than in adults, but had lower values of CT

The marked increase and the high levels of CT found in the newborn infant can be compared with the findings of Anast on artificially fed rats (5). He concluded that there is a direct relationship between high calcium intake and a high metabolic activity in the ultimobranchial body (which secretes CT) and that there is an inverse relationship between high calcium intake and the metabolic activity of the parathyroid glands. A hypercalcemia exists in utero. This might give, after birth, in the newborn infant a hyperfunction of the C-cells in the ultimobranchial body with high levels of CT and a hypofunction of the parathyroid glands with low levels of parathyroid hormone.

CT lowers plasma calcium by inhibiting the mobilisation of calcium from the bone (48). This effect of CT is more marked when there is a high bone turnover of calcium (41). A significant negative correlation between CT and calcium in plasma

is to be found in such cases. Such a correlation was found in IDM but not in the controls.

During the period when CT increased in plasma low levels of PTH were seen (Fig. 4 Paper III). This is in agreement with the findings of Tsang et al. (54). However no indications of hyperparathyroidism in the diabetic mothers were found as suggested by Tsang et al (52). In only one of the five infants investigated was an increase in the PTH-concentration seen, despite decreasing calcium values. This infant was an IDM who developed clinical signs of NHC (Fig. 5 Paper III). The only effect of the increase of PTH was a phosphaturia with a concomitant decrease of plasma phosphorus. Total calcium actually decreased further in spite of an increased PTH level and the symptoms of NHC persisted. This situation mimics an end-organ unresponsiveness to PTH and may be due to a block of calcium resorption from bone caused by the higher CT levels. CT competes with PTH at the bone cells but not at the kidney (41).

E. Growth hormone during the first day of life in infants of diabetic mothers and normal infants and its relation to calcium in plasma.

The secretion of GH is stimulated both by hyperglycemia and hypoglycemia (16 30 37).

Because of their hyperinsulinism IDM have a greater risk of developing hypoglycemia. Because of that they are often given glucose infusion or a forced caloric intake immediately after birth in many departments.

Hypocalcemia often appears together with a hypoglycemia and it is well known that hypocalcemia can be treated by the administration of glucose. An explanation for this seems, however not to appear in the literature.

In order to investigate this and the importance of GH for the decrease of plasma calcium and for developing NHC the following study was designed.

Four normal infants delivered vaginally and six of the IDM presented in Paper III were studied.

The normal infants received no glucose after birth and were allowed to take breast milk ad libitum (both the time of eating and the amount taken were left up to the infants themselves). The six IDM were given a glucose infusion immediately after birth and were early and intensively fed as described in Paper III.

All control infants were full-term and normal with no asphyxia after birth and none developed signs of NHC.

Blood samples were taken at the following time intervals: cord blood 1 3 4-8 and 21 36 hours after birth. The blood sample was omitted when there were difficulties in blood sampling (e.g. multiple attempts at venous puncture) since stress stimulates GH secretion. Ca-tot, GH and blood sugar were determined in all blood samples. The amounts of plasma were too small to allow determinations of Ca-uf CT and PTH in the control infants.

In IDM a marked increase in the concentration of *GH* was seen after birth as shown in Fig. 7 Maximum levels were reached at 4-8 hours of age The mean increase from birth up to 4-8 hours of age was 20 mU/l. In the controls, on the contrary no particular change was seen up to 4-8 hours of age At 4-8 hours of age the concentration of GH was significantly higher in IDM than in the controls ($p<0.005$). In cord blood the mean level was higher in IDM than in the controls, but the difference was not statistically significant.

After 4-8 hours of age and up to 21 36 hours of age a decrease in the concentration of GH was seen in IDM.

In the controls a marked increase in the concentration of GH took place after 4-8 hours of age

Fig. 7 Growth hormone during the first day of life in IDM and in normal infants.

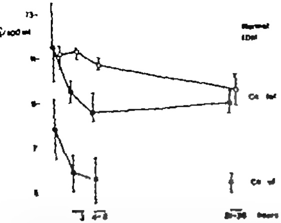


Fig. 8. Total and ultrafiltrable calcium in plasma in IDM and total plasma calcium in normal infants during the first day of life. (All values of Ca-uf are corrected to the actual pH of the infants at the moment of blood sampling).

and maximum levels were reached at 21 36 hours of age. No significant difference was seen between the control infants and IDM at 21 36 hours of age.

As shown in Fig. 8 a marked decrease was seen after birth in both Ca-tot and Ca-uf in IDM up to 4-8 hours of age. After that no particularly change was seen in either Ca-tot or Ca-uf up to 21 36 hours of age.

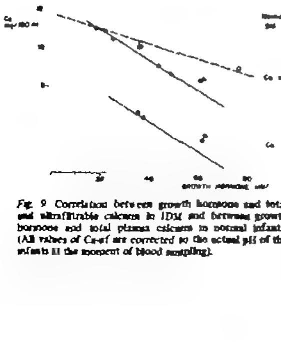


Fig. 9. Correlation between growth hormone and total and ultrafiltrable calcium in IDM and between growth hormone and total plasma calcium in normal infants. (All values of Ca-uf are corrected to the actual pH of the infants at the moment of blood sampling).

The control infants showed no clear-cut trend up to 1 3 hours of age while thereafter a decrease was seen up to 21 36 hours of age.

The concentration of Ca-tot was significantly higher in the control infant at 1 3 and 4-8 hours of age ($p<0.05$ and $p<0.005$ respectively) than in the IDM. In cord blood and at 21 36 hours of age no significant differences were seen.

A significant negative correlation was found between GH and both Ca-tot and Ca-uf in IDM ($p<0.05$) as seen in Fig. 9. This figure also shows that the two regression lines were parallel. A significant negative correlation between GH and Ca-tot was also seen in the control infants as demonstrated in the same Fig. ($p<0.005$). As seen in Fig. 9 the regression line for IDM appears to be somewhat steeper than that for the control group.

DISCUSSION

The rate of bone turnover is high when the concentration of GH is increased (41). The input of calcium to the skeleton would therefore be increased with an increase in GH concentration.

In the present study a marked increase in the concentration of GH was seen in both IDM and in the controls.

Concomitantly with the increase of GH a decrease of plasma calcium was seen in both IDM and controls and a significant negative correlation between GH and Ca-tot was found in both IDM and controls. In IDM where Ca-uf was determined such a correlation was also found between GH and Ca-uf.

On the basis of these findings it might be postulated that an increase in GH concentration in the newborn infant after birth lowers plasma calcium because of an increased input of calcium to the skeleton due to an increased rate of bone turnover. A higher sensitivity to CT is expected in this situation (Paper III), since the result of the inhibiting effect of CT on resorption of calcium from the bone cells will be higher when the input of calcium in the skeleton is high.

GENERAL DISCUSSION AND CONCLUSIONS

Determinations of Ca-uf have been used in these studies. As most of the Ca-uf fraction consists of ionized calcium, a determination of Ca-uf can be used as a measure of ionized calcium The concentration of ionized calcium and thereby also the Ca-uf fraction is highly pH-dependent. This is seen in the dissociation curve (Paper I) which shows that pH has its greatest effect on the distribution of plasma calcium within the pH range compatible with life. It is obvious from this curve that an increase in pH will give a marked decrease in Ca-uf This decrease of Ca-uf is due to a decrease of ionized calcium which is bound to the plasma proteins. A decrease in ionized calcium and thereby also in Ca-uf may thus occur without any change in Ca-tot. It is therefore not surprising that a discrepancy between clinical signs of NHC and total plasma calcium is noted in the literature (12, 17 35 45 50). Determinations of Ca-uf might therefore be a better means of diagnosing NHC than total plasma calcium, as is also shown in Papers II and III. It was also shown in these papers that all infants with clinical signs of NHC had a value of Ca-uf at or below 5 0 mg/100 ml plasma. No clear-cut limit for Ca-tot was found

Direct measurement of ionized calcium would be the best method for diagnosing NHC. The literature present reports in which selective calcium electrode have been used. The limits for the appearance of NHC are, however variable with a range from 2.8 to 3.5 mg/100 ml plasma (11 40 42).

Since it is possible, using the curve shown in Paper I to recalculate a determined value of Ca-uf to the actual value at the moment of blood sampling knowing the actual pH, it has been possible to study the exact time-course of the decrease of Ca-uf in the newborn infant (Paper II and III).

The decrease of plasma calcium that develops after birth has been regarded as a physiological hypocalcemia (21). Craig and Buchanan (17) stated in 1958 that »hypocalcemic tetany per se occurring within 36 h after birth should be regarded as an exaggeration of a normal physiological state rather than as a distinct abnormal clinico-biochemical entity». Why this exaggeration occurred and in some infants, especially in IDM more than in others was not established.

To date no definite mechanism has been reported in the literature explaining why early NHC develops after birth.

The present studies were designed to define this mechanism. These studies have shown that.

At birth the newborn infant has a certain plasma calcium concentration as a starting value (Figs. 2 4). This concentration is dependent on the plasma calcium in the mother as shown by the significant correlation found between mother and infant at birth in the study of mother-infant relation (Table I). As was also shown in that study infants delivered vaginally had higher starting values than infants delivered by cesarean section (Fig. 2, Table II). This was probably due to the fact that there mothers were not in a fasting state

During the last 2 3 months of fetal life the deposition of minerals including calcium rises steeply Approximately 140-280 mg of calcium is deposited daily during the last 2 months of pregnancy (53). The normal full-term newborn infant will thus have a well mineralized skeleton at birth. During fetal life IDM have been exposed to prolonged hyperglycemia. A prolonged hyperglycemia in IDM in utero has been shown by Turner et al. (55) to depress the secretion of GH. It may therefore be postulated that IDM are born with a skeleton that is not well-mineralized as a result of a low bone turnover during fetal life due to a decreased GH secretion. The higher the concentration

of GH the higher is the bone turnover (41). The normal infant in contrast to IDM has higher levels of GH during fetal life which explains the ability to deposit a large amount of calcium during fetal life.

During fetal life the infant has a hypercalcemia. According to Anast (5) there is a direct relationship between high concentration of calcium and the metabolic activity of the ultimobranchial body (which produces CT) and conversely there is an inverse relationship between high concentration of calcium and the metabolic activity of the parathyroid glands. At birth the newborn infant will therefore have hypofunctioning parathyroid glands which was also found in the present study (Paper III). This is in agreement with the findings of Tsang et al. (54). The C-cells in the ultimobranchial body which produce CT will be saturated with CT for the same reason.

After birth and up to the first meal (6-10 h of age) the infant has no supply of calcium. The demands for calcium from the tissues and skeleton are high and are higher the less saturated the skeleton is with minerals. During this time there is also seen a marked decrease in Ca-tot and Ca-uf in plasma in all infants studied, but most marked in IDM (Figs. 1 and 2, Paper III Figs. 3 and 4). If at the same time an increase in pH occurs the decrease in Ca-uf will be more marked than the decrease of Ca-tot as more ionized calcium is bound to the plasma proteins (Fig. 5) as in IDM.

The high levels of free cortisol found in cord plasma by Aarskog (1) can not explain this decrease of plasma calcium as cortisol decreases plasma calcium by increasing the secretion of calcium in the urine and no urinary calcium was found in the present study. As no calcium was given orally the inhibiting effect on the resorption of calcium from the gut by cortisol is also excluded as the cause of the decrease of plasma calcium.

In spite of the fact that pH decreases in both the lower and the higher group immediately after birth (Fig. 5) Ca-uf decreases in both. After 4-8 hours of age all groups were similar in pH. The infants who had a lower starting value of Ca-uf at birth showed a decrease parallel with those who had a higher starting value (Fig. 4). It seems therefore that these infants do not have a higher demand for calcium, but they reached lower levels of calcium just because they had lower starting values (Paper II). The reason for the lower starting value could be explained in some cases (6 7 9 Paper II) by placental insufficiency (32). The difference in pH at birth between the lower and the higher group was not significant and cannot explain the significant difference in Ca-uf between the higher and the lower groups. In Figs. 3-6 the two groups are compared with IDM and normal infants delivered vaginally (Paper III). The lower group follows very closely in Ca-uf the values of IDM (Fig. 4) and both these groups are significantly different from the higher group which seems to follow the values of the normal infants delivered vaginally. The same trend holds true for Ca-tot but the differences did not reach statistical significance. This might indicate that the lower group runs a higher risk of developing NHC, which is true for IDM.

Both GLI and glucagon stimulates the secretion of CT (7 13).

A marked increase in the concentration of CT was seen after birth and maximum levels were reached at 24 hours of age (Paper III).

Both hyperglycemia and hypoglycemia stimulate the secretion of GH (16 30, 57). In the present study such an increase of GH was found. The higher the concentration of GH the higher is the bone turnover (41). A significant negative correlation was found between GH and plasma calcium in the present study (Paper V). The higher the bone turnover is due to an increased concentration of GH the higher would therefore the input of calcium in the skeleton be. CT decreases plasma calcium by inhibiting the resorption of calcium from the bone (48). The higher the bone turnover and thereby the input of calcium in the skeleton is the higher would therefore the sensitivity to CT be. The higher the sensitivity to CT the more marked is the decrease of Ca-tot in plasma and a significant negative correlation between CT and calcium in plasma is to be found. Such a significant negative correlation was found in IDM in this material (Paper III).

An infant who during the first days of life, when the concentration of CT is elevated is given a glucose infusion might therefore have a higher risk of developing NHC. This is true for IDM. It is also true for IRDS, who because of their respiratory problems are given glucose infusion (Fig. 6, Table III).

As an increased concentration of phosphorus potentiate the inhibiting effect of CT on the resorption of calcium from bone (41), an increase in the concentration of phosphorus during the first days of life will further decrease plasma calcium. This can explain why in previous studies it was suggested that an increased concentration of phosphorus was the whole cause of NHC.

The newborn infant s ability to normalize a low plasma calcium might be small, as low levels of PTH were found after birth in comparison with adult standards (Paper III). Low levels of PTH after birth have recently also been found by Tsang et al. (54). Even when an increase of PTH was seen, as in one case in Paper III, no increase of plasma calcium was noted since the high concentration of CT competetively inhibits the low concentration of PTH at the bone cells. The only effect of PTH that was seen was a phosphaturia with a concomitant decrease of the concentration of plasma phosphorus. CT does not compete with PTH at the kidney (41). These results mimic an endorgan unresponsiveness to PTH which has been suggested by Bakwin (8), Brown et al. (11) and Conelly et al. (15) to be the cause of NHC. These findings can also explain why Tsang et al. (52) found an increase in the urinary concentration of phosphorus at this age.

A possible mechanism for the development of early NHC can be suggested from the results of these studies (Paper IV). First the infant lost the active transport of calcium across the placenta. During the first hours of life the infant does not receive any calcium orally and the decrease of calcium is due solely to the input of calcium into the tissues and skeleton. After 4-8 hours an increase in the concentration of CT occurs probably stimulated by an increased secretion of glucagon and/or GLI. CT decreases plasma calcium where there is a high bone turnover by inhibiting the resorption of calcium from the bone cells. Stress as well as hyper or hypoglycemia stimulate secretion of GH. An increase in the concentration of GH increases bone turnover and thereby increases the input of calcium in the skeleton. The higher the bone turnover the higher will therefore the effect of CT be.

Thus newborn infants with a hyper or hypoglycemia or receiving an infusion of glucose solution during the first day of life are liable to develope NHC.

As the infant is born with a hypofunction of the parathyroid glands a low plasma calcium cannot be normalized as the low concentration of PTH cannot compete with the high concentration of CT on resorption of calcium from the bone cells. The low level of plasma calcium persists.

CONCLUSION

An infant with a low calcium intake and a high concentration of phosphorus, who gets an increase in the concentration of GH due to a glucose infusion or a prolonged hypoglycemia during the first day of life when the concentration of CT is high and PTH is low should be more liable to develop NHC.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to

Professor Petter Karlberg, Head of the Pediatric Department I, for his valuable support and constructive criticism,

Professor Björn Isaksson, Head of the Institute of Clinical Nutrition, who introduced me to the field of calcium research,

Ingemar Kjellmer M.D for valuable discussions, encouragement and great interest for my work and

Mrs Ulla Eriksson for excellent technical assistance.

These studies were supported by grants from the Medical Faculty of the University of Göteborg, the Medical Society of Göteborg, Första Majblommans Riksförbund of Sweden and Fels Fellow in Pediatric Research, the Fels Research Institute for the Study of Human Development, Yellow Springs, Ohio 45387

REFERENCES

1 Aarskog, D. Cortisol in the newborn infant. *Acta Paediat Scand*, Suppl. 158, 1965

2. Acharya, P T & Payne W W Blood chemistry of normal full-term infants in the first 48 hours of life. *Arch Dis Child*, *40* 430, 1965

3 Almqvist, S., Telenius, M. & Wästhed, B. Radioimmunoassay for human serum calcitonin. *J Clin Invest*, in press, 1974

4 Almqvist, S. & Wästhed B. A radioimmunoassay for human parathyroid hormone in serum and some clinical applications. *Acta Endocrinol (Kbh)* in press, 1974

5 Anast, C.S. Clinical and experimental studies related to parathyroid hormone and calcitonin. *Proc 13th Int Congr Paediat* Wien, 1971 vol. 8 p p. 117

6. Anderch, M. & Oberst, F W Filtrable serum calcium in late pregnant and parturient women, and in the newborn. *J Clin Invest*, *15* 131 1936.

7 Avioli, L.V., Birge S.J., Scott, S. & Shieber W Role of the thyroid gland during glucagon-induced hypocalcemia in the dog. *Am J Physiol*, *216* 939 1969

8. Bakwin, H. Pathogenesis of tetany of the newborn. *Am J Dis Child* *54* 1211 1937

9 Bloom, S.R. & Johnston, D.J Failure of glucagon release in infants of diabetic mothers. *Br Med J* *4* 453 1972.

10. Bold A.M. Measurement of dialysable calcium. An automated method for estimating the diffusible fraction of calcium in plasma. *VIIth Int Congr of Clin Chemistry* Geneve sept, *1969* p. *376*.

11 Brown, D.M. Boen, J & Bernstein, A. Serum ionized calcium in newborn infants. *Pediatrics*, *49* 841 1972.

12. Bruck, E. & Weintraube, D.M. Serum calcium and phosphorus in premature and full-term infants. *Am J Dis Child*, *90:* 653 1955

13 Böttger I., Faloona, G.R. & Unger R.H. The effect of calcium and other salts upon the release of glucagon-like immunoreactivity from the gut. *J Clin Invest* *51* 831 1972.

14 Cadranel S. & Loeb H. Energetic metabolism in newborns of diabetic mothers. *Proc 13th Int Congr Paediat*, Wien, 1971 vol. 7 p p. 473

15 Connelly J.P Crawford, J.D. & Watson, J Studies of neonatal hyperphosphatemia. *Pediatrics, 30* 425 1962.

16 Cornblath, M., Parker M.L. Reisner S.H. Forbes, A.E. & Daughaday W.H. Secretion and metabolism of growth hormone in premature and full-term infants. *J Clin Endocrinol Metab 25* 209 1965

17 Craig, W.S. & Buchanan M.F G. Hypocalcemic tetany developing within 36 hours of birth. *Arch Dis Child 33* 505 1958

18. David L. & Anast, C. Serum immunoreactive calcitonin (ICT) *in newborns. Pediatr Res, 7* 386 1973

19 Delivoria-Papadopoulos, M., Battaglia, F C. Bruns, P D & Meschia, G Total, protein-bound, and ultrafiltrable calcium in maternal and fetal plasmas. *Am J Physiol, 213* 363 *1967*

20. Fanconi, A. & Prader A. Hypocalcemic fits in neonates. *Lancet 1* 864 1968

21 Fanconi, A. Hypokalzämie im Kindersalter *Praxis, 56 271 1967*

22. Gardner L.I., Mac Lachlan E.A., Pick, W., Terry M.L. & Butler A.M. Etiologic factors in tetany of newly born infants. *Pediatrics, 5 228 1950.*

23 Gershanik, J.J., Levkoff A.H & Duncan, R. The association of hypocalcemia and recurrent apnea in premature infants. *Am J Obstet Gynecol, 113* 646 1972.

24 Gittleman, I.F Pincus, J.B., Schmertzler B.S. & Annecchiarico F Diabetes mellitus or the prediabetic state in the mother and the neonate *Am J Dis Child 98* 342, 1959

25 Gittleman, I F., Pincus, J B., Schmerzler E. & Saito, M. Hypocalcemia occurring on the first day of life in mature and premature infants. *Pediatrics, 18.* 721 1956

26 Hardie, G., Harrison, V C. & Kench, J.E. Further observations on serum proteins in respiratory distress syndrome of the newborn. *Arch Dis Child, 43* 471 1968.

27 Heach, R.D., Woodhead S., Huefner M & Wolf H. Gastrointestinal stimulation of calcitonin in adults and newborn. *Horm Metab Res, 5* 235 1973

28. Hohenauer L., Rosenberg, T.F & Oh, W Calcium and phosphorus homeostasis on the first day of life. *Biol Neonate, 15* 49 1970.

29 Howland, J & Marriott, W.M. Observations upon the calcium content of the blood in infantile tetany and upon the effect of treatment by calcium. *Q J Med 11* 289 1917

30. Humbert, J.R. & Gotlin, R.W Growth hormone *levels in* normoglycemic and hypoglycemic infants born small for gestational age. *Pediatrics, 48.* 190 1971

31 Khattab A.K. & Forfar J O.. Interrelationships of calcium, phosphorus and glucose levels in mother and newborn infant. *Biol Neonate, 15* 26 1970.

32. Khattab A.K. & Forfar J O. The interrelationship between calcium, phosphorus and glucose levels in mother and infant in conditions commonly associated with »Placental Insufficiency». *Biol Neonate, 18* 1 1971

33 Keen, J.H. Significance of hypocalcemia in neonatal convulsions. *Arch Dis Child, 44* 356 1969

34 Kehrer E. Die geburtshilflich-gynäkologische Bedeutung der Tetanie *Arch Gynækol, 99* 372, 1913

35 Keuth, U & Kremers, H. Untersuchungen *zur Ursache der neonatalen Tetanie. Monatsschr Kinderheilkd, 117* 268 1969

36. Paupe, J., Colin J Politis, E. & Lelong, M. Some physiological variations of blood calcium level in mothers during labour in cord and newborn infants. *Biol Neonate 3* 357 1961

37 Payne W W & Acharya, P T The effect of abnormal birth on blood chemistry during the first 48 hours of life. *Arch Dis Child 40*· 436 1965

38 Pedersen, K.O. Determination of calcium fractions of serum. I. The separation of pro-

tein-bound and protein-free fractions by means of a simplified ultrafiltration technique. *Scand J Clin Lab Invest 24* 69 1969

39 Radde I.C., Parkinson, D.K. & Höffken, B.. Ionized calcium levels in the healthy and diseased neonate. *Proc 13th Int Congr Pediatr* Wien, 1971 vol. 7 p p. 363

40. Radde I.C., Parkinson, D.K., Höffken, B., Appiah, K.E. & Hanley W B. Calcium ion activity in the sick neonate Effect of bicarbonate administration and exchange transfusion. *Pediatr Res, 6* 43 1972.

41 Rasmussen, H.. Parathyroid hormone thyrocalcitonin and related drugs. *Intern encyklopedia of pharmacology and therapy* Section 51 vol. 1 1970.

42. Riegel, K. & Harms, W Die Plasma-Calcium-Fractionen des Neugeborenen und ihre Abhängigkeit von Änderungen des Säure-Base-Stoffwechsels. *Monatsschr Kinderheilkd, 116* 265 1968.

43 Robertson, W G. & Peacoch, M. New techniques for the separation and measurement of the calcium fractions of normal human serum. *Clin Chim Acta, 20* 315 1968.

44 Rose, V Infants of diabetic mothers: Clinical and pathological features in a series of 25 cases. *Can Med Assoc J 82* 306, 1960.

45 Rosenkranz, A.. Serumkalzium-Spiegel beim Frühgeborenen in den ersten Lebenstagen. *Paediatr Paedol, 2.* 367 1966.

46. Saville P.D. & Kretchmer N Neonatal tetany: A report of 125 cases and review of the literature *Biol Neonate, 2* 1 1960.

47 Shannon, W.B.. Generalized edema in association with tetany of the newborn. *Arch Pediatr 46* 549 1929

48. Talmage R.V., Anderson, J.J B & Cooper C.W The influence of calcitonins on the disappearance of radiocalcium and radiophosphorus from plasma. *Endocrinology 90*: 1185 1972.

49 Thalme B. Electrolyte and acid-base balance in fetal and maternal blood. *Acta Obstet Gynecol Scand (Suppl) 8,* 1967

50. Thalme B., Engström, L., Broberger U., Edström, K. & Kretzschmar G. Infants of diabetic mothers. II. Acid-base and electrolyte balance during the first 48 hours after birth. *Acta Paediat Scand, 61* 315 1972.

51 Thalme, B.. Potassium, sodium chloride, total protein, calcium and inorganic phosphorus in plasma of human foetuses and newborn infants. *Biol Neonate, 18* 444 1971

52. Tsang, R.C Kleinman, L.I., Sutherland, J.M. & Light, I.J Hypocalcemia in infants of diabetic mothers. *J Pediatr 80*: 384 1972.

53 Tsang, R.C. & Oh, W Neonatal hypocalcemia in low birth weight infants. *Pediatrics, 45* 773 1970.

54 Tsang, R.C Chen, I.W., Friedman, M.A. & Chen, I. Neonatal parathyroid function. Role of gestational age and postnatal age. *J Pediatr 83* 728, 1973

55 Turner, R.C., Cahley N.W & Beard, R.W Human fetal plasma growth hormone prior to the onset of labour. Effects of stress, glucose arginine and maternal diabetes. *Biol Neonate, 22* 169 1973

56. Twardock, A.R. & Austin, M.K. Calcium transfer in perfused guinea pig placenta. *Am J Physiol, 219* 540, 1970.

57 Westphal, O Human growth hormone. A methodological and clinical study *Acta Paediat Scand (Suppl) 182,* 1968.

58. Will, H. Die Neugeborenen in Spasmophilie. *Monatsschr Kinderheilkd 80*: 309 1939

59 Zetterström, R. & Arnhold R.G Impaired calcium-phosphate homeostasis in newborn infants of diabetic mothers. *Acta Paediat 47* 107 1958.

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SUPPLEMENT 250 1974

HEART RATE VARIATION IN INFANTS WITH THE RESPIRATORY DISTRESS SYNDROME

BY PENTTI KERO

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HEART RATE VARIATION IN INFANTS
with
THE RESPIRATORY DISTRESS SYNDROME

ACTA PAEDIATRICA SCANDINAVICA
SUPPLEMENT 250, 1974

From the Cardiorespiratory Research Unit and the Department of Paediatrics, (Head, Professor T. Peltonen, M.D.) University of Turku, Turku, Finland

HEART RATE VARIATION IN INFANTS with THE RESPIRATORY DISTRESS SYNDROME

BY
PENTTI KERO

Vammala 1974. Vammalan Kirjapaino Oy

CONTENTS

Vammala 1974. Vammalan Kirjapaino Oy

ABBREVIATIONS

A	Adrenaline
CA	Cathecolamine
CHD	Congenital heart disease
CPAP	Continuous positive airway pressure
CRT	Cathode ray tube
CV	Coefficient of variation for the RMSM
CVS	Coefficient of variation for the RMSSD
EEG	Electroencephalography
ECG	Electrocardiography
FHR	Fetal heart rate
g	Gram
HMD	Hyaline membrane disease
hr	Hour
Hz	Herz
IPPR	Intermittent positive pressure respiration
kPa	KiloPascal
min	Minute
msec	Millisecond
MSD	Mean successive difference
mV	Millivolt
NA	Noradrenaline
NHR	Neonatal heart rate
P O_2	Arterial oxygen tension (kPa)
RDS	Respiratory Distress Syndrome
RMSM	Root mean square of differences from the mean (overall variation)
RMSSD	RMS-value of successive differences
SD	Standard deviation
sec	Second

Group »CS	Infants delivered by caesarean section
Group NonCS»	Vaginally delivered infants
Group D	Infants of mothers with diabetes mellitus
Group NonD»	RDS infants of non-diabetic mothers
Group DC	Decerebrated children
Group EX	Expired infants
Group NonEX	Surviving infants
Group Ict»	Icteric infants
Group NonIct	Nonicteric infants
Group Pn	RDS infants developing pneumothorax
Group T	RDS infants of toxaemic mothers
Group NonT	RDS infants from nontoxaemic pregnancies

INTRODUCTION

In recent years a considerable interest has been focused on the respiratory distress sydrome (RDS). There is, however confusion regarding the etiology and even regarding the terminology of the disease. The term Idiopathic respiratory distress of the newborn or in short, RDS has been used. This is the clinical counterpart of the disease characterized by the pathologist as a hyaline membrane disease, HMD RDS is still the most usual cause of death of newborn infants (38) Also many of the surviving RDS infants have some neurologic abnormalities inspite of the remarkably advanced possibilities to predict and treat the RDS In the modern ...nsive care of neonates various parameters can be analysed, such as the lecithin sphingomyelin ratio from the amniotic fluid (42) chest X ray blood gas analysis etc., but in many cases the diagnosis based on these techniques is too late for an efficient therapy It would be important to find a method with which we could predict the probability of RDS in an infant.

Nowadays when long term recording system have been developed a considerable variation in the heart rate of newborn infants has been documented (83 125 132, 134 136). With the development of digital computers and a statistical analysis of the series of intervals it has become possible to find quantitative differences in the heart rate variation peculiar to some pathological conditions like the RDS The fixation of the heart rate has been described in active RDS by many investigators (107 128, 132, 133). Thus an early detection of a decreased heart rate variation could be a predictive sign of RDS.

THE PURPOSE OF THE PRESENT INVESTIGATION

The purpose of the present investigation was

1) To investigate if it would be feasible to computerize the monitoring of the heart rate in an intensive care neonatal ward.

2) To use long-term monitoring of the ECG and an automatic analysis of the heart rate to quantify the degree of heart rate variation in infants with the respiratory distress syndrome.

3) To study if the heart rate patterns found could be utilized in a clinical characterization and prediction of the state of developing RDS.

REVIEW OF LITERATURE

RESPIRATORY DISTRESS SYNDROME (RDS) IN NEWBORN INFANTS

Etiology of RDS

Old hypotheses

Many factors have been suggested which can be an etiologic reason for or which can influence the development of RDS The old hypotheses have included a patent ductus arteriosus (32) which is not true according to others (97) congestive heart failure (15 33 80), a decreased blood volume (57 114, 117 131) placental transfusion (87 131 149 150), disturbances in the fibrinolysin system (3 37 78) oxygen toxicity (94, 109 118, 146) a low total plasma protein in RDS infants (12, 48, 79) and the capillary erection theory of Jäykkä (58, 59)

Current concepts of the development of RDS

According to many authors (6 7 16 103) RDS is quite closely associated with prematurity Besides prematurity two theories of the etiology of RDS are under active investigation

a) Pulmonary hypoperfusion

Chu et al and others (24, 25 66 67) believe that in RDS there is a reflex vasoconstriction as a response to some stress during or after the delivery This regulation tends to centralize the circulation and tends to preserve the blood flow to the brain, heart and placenta at the expence of the flow to other organs like the lungs (33, 76 97) The synthesis and secretion of the pulmonary surfactant may decrease in severe vasoconstriction (41, 105 141).

In autopsies of RDS infants there is evidence of an increase in the precapillary pulmonary resistance (40, 68, 69) Pulmonary vasoconstriction in response to hypoxia and acidosis could be a cause of the pulmonary hypoperfusion. Many agents such as histamine and polypeptide B have been suggested to be involved in this vasoconstriction (14). RDS is a multistaged, multifunctional infantile form of shock. It is an expression of general peripheral hypoperfusion resulting in systemic hypotension, decreased cardiac contractility and pulmonary atelectasis and hypoperfusion (93)

b) Deficient alveolar lining layer (Surfactant)

Nowadays it is certain that the RDS is related to the primary absence, deficiency or alteration of the highly surface-active alveolar lining material (the pulmonary surfactant) (7 8, 70 106). One of the reasons for this may be the vasoconstriction of the pulmonary arteries seen in RDS (68) The pulmonary surfactant is a complex material that lines the alveoli of the lung (7 8, 68, 141).

It is possible that in some immature infants the primary disorder is a surfactant deficiency while in larger infants, who suffer from intrauterine asphyxia, the primary trigger could be pulmonary vasoconstriction (7). Another possibility is that in each infant the etiology could involve varying degrees of surfactant deficiency and pulmonary vasoconstriction (69 141) According to Peltonen et al (99) the disorder may be in the absorption of the tracheobronchial fluid reflecting (partly) the pulmonary vasoconstriction.

However the major pathologic changes in the idiopathic respiratory distress syndrome include collapse of the terminal air spaces and formation of hyaline membranes in the respiratory bronchioles (41, 69). Alveolar collapse seems to be related to a lack of a surface tension-reducing substance (surfactant), which is considered to be derived from alveolar inclusion bodies (68 141) During and after the labour the infants may have an abnormality in the release of surfactant to the alveolar surface (7 126).

Physiological abnormalities in RDS

The infant who develops RDS begins to breath like a healthy infant (5 6 16) The high negative intrathoracic pressure increases until the lungs snap open. But the lung volume and alveolar ventilation starts to decrease in the RDS infant. The lungs fail to expand as fully as other lungs static pressures of 35 cm H_2O which are sufficient to fully inflate a normal lung, permit only a small volume of air to enter the lung of an infant with RDS, and most of this air is in the bronchioles (46) This is true especially regarding premature infants (6). Peltonen et al (100) have noted that the pulmonary circulation also has a remarkable effect on the pressures which are needed to open the lungs. The lung compliance is also reduced. The infant does not retain residual air upon expiration and his lungs collapse and this produces hypoxia (60 93, 105 127).

The pulmonary capillary flow is decreased and about 30—60 / of the cardiac output is shunted from the right to the left (114). Acidosis still diminishes the pulmonary blood flow and also the surfactant production and promotes further collapse (39 93). Hypoxia increases the capillary permeability and helps to promote transudation of fluid into the myocardium, alveoli and other tissues (40, 122). Fibrin forms the matrix, which entraps the necrotic alveolar duct epithelium, the red cells, protein etc. These then coalesce to form the hyaline membranes lining the alveolar ducts and terminal bronchioles (40). Transudation to the alveoli can also destroy the surfactant (34, 41 68, 69 70).

P thologic anatomic findings in RDS

At autopsy the lungs of the infants with RDS are solid, airless, dark red and liver like (40, 68). There is varying widespread atelectasis and overdistended alveoli (68, 69). Also the lymphatics are dilated (70 95) and damage of the alveolar epithelial cells and swelling of the capillary endothelial cells is seen. Hyaline membranes often appear in RDS and the osmiophilic bodies are decreased in the alveolar II cells (6, 41, 68, 69 70).

According to Gandy et al (40) the capillaries directly beneath the hyaline membranes are often filled with tightly packed red cells in RDS infants. In contrast, the capillary bordering areas unaffected by the hyaline membrane are wide open and contain plasma as well as discrete red cells like those in normal lungs. Also other investigators have shown disturb-

ances in the small muscular arteries and especially the pulmonary arterioles in infants with RDS (68, 69). The pulmonary venous vasculature does not seem to be the most important primary obstructive factor in the lungs of RDS infants (69)

Significant clinical features of RDS

The symptoms and signs of RDS in neonates can vary very much, but the following features are considered typical for RDS infants according to many authors (5, 6, 16, 103 106 119 127)

a) Early onset of difficulties in breathing after the delivery
b) Cyanosis is almost always associated with RDS
c) Retraction of the chest
d) Grunting in the early stages of RDS
e) Tachypnea or apnea
f) Decreased chest volume
g) Acidosis
h) Peripheral edema
i) Air entry poor and breath sounds distant
j) Reticulogranular appearance and air bronchogram in chest X-ray (18, 112, 145 146)

ELECTROCARDIOGRAPHY (ECG) AND HEART RATE IN NEWBORN INFANTS

ECG in RDS and asphyctic infants

A number of paediatric electrocardiographic studies has been performed (82, 90, 91, 108, 134, 142, 143) and some typical ECG features of healthy infants have been documented. the neonatal P waves are higher than those of older children (90 91) right ventricular preponderance which later in childhood turns into left ventricular dominance and inverted T waves in the precordial electrocardiogram (90 108)

In the electrocardiogram of premature infants some features differ from that of term infants· the electric axis of the heart deviates to the right, but the angle of deviation is often smaller during the first weeks of life in prematures than in term infants (108) and low voltage in the QRS complex and also in the P and T waves (91 134) is seen.

The ECG of asphyctic infants also shows peculiar features. In the ECG of asphyctic infants : extrasystoles, conduction defects, A V blocks and prolongation of the QRS duration have been described (107 129 134). Sutin et al (124) have reported peaked and notched P waves in RDS and Usher (129) has found broadening and flattening of the P wave. However according to Keith et al (62) the differences in the ECG of the asphyctic and the normal infant are small and it is not possible to diagnose the RDS on the basis of the ECG

Left ventricular preponderance was an electrocardiographic feature of the asphyctic newborns in the study of Usher (129) In the investigation of Keith et al (62) low pulmonary vascular resistance and an open ductus arteriosus were associated with this pattern. In RDS with right ventricular dominance the patients had a high pulmonary resistance and an open ductus: the prognosis was better for the latter cases (62). Sutin et al made the same observation (123)

S-T deviation and pathological T waves in RDS infants have been mentioned by Ahvenainen and Landtman (2), Usher (129) and Keith et al (62). They believed that these changes result from metabolic and electrolyte alterations, caused by asphyxia in the myocardial cells.

Continuous electrocardiography

In conventional ECG recordings only a short segment of the electric activity of the heart is examined. Thus most of the information about this dynamic signal is missed. This disadvantage was eliminated by the invention of long-term ECG monitoring techniques and the rapid analysis equipment of Holter in 1961 (53).

Computer analysis of long-term ECG registration

A beat-by-beat analysis of the ECG with a computer is a very demanding task. On the other hand, utilization of a stochastic point process analysis in the characterization of the heart rate is nowadays feasible. Procedures to study dynamic alterations in the cardiac action have improved remarkably in recent years due to the development of the computer analysis (26 27 110). The analysis system have since then been developed further by Rautaharju and his group (102, 123 135 147)

Heart rate variation in healthy newborn infants

Basal heart rate in the fetus and newborn infants. In several studies it has been reported that there are transient variations in the fetal heart rate during the pregnancy and during the delivery (11 17 54, 55). Some of these transient changes, especially those reflecting a deceleration of the heart rate, seem to have a particular prognostic significance (17 54) Here are some typical changes also after the delivery in the heart rate of the infant (Table 1).

The heart rate of small premature infants seems to be significantly higher than that of larger ones, but no difference exists between the mean basal heart rate of term and premature infants (136, 143).

Respiratory heart rate variation. According to Urbach et al respiration produces heart rate changes of short duration in most children (128). Vallbona et al found respiratory fluctuations in the heart rate to be usual (139). They were unrelated to the level of the heart rate. Tarlo and Välimäki studied heart rate patterns and apnea in newborn infants and found that healthy term babies also have a tendency to apneic bradycardia (125)

Cry pattern in the heart rate. The infant's cry is usually accompanied by tachycardiac fluctuation according to Vallbona et al (138) and Urbach et al (128)

Gribbe et al (45) have shown that because the infant has very little residual volume in the heart he cannot increase the stroke volume, consequently the young

Table 1 Heart rate after the delivery in healthy newborn infants.

The ages of the infants

1 min beats per min	30—60 min beats per min	1—6 hrs beats per min	1 day beats per min	1 day—1 wk beats per min	Reference
174	134	125	120	slight increase	Vallbona (139)
	125	120	130		Välimäki (134)
170	142				Cordero (30)

heart can meet increased requirements only by increasing the heart rate.

Bradycardia and tachycardia. Periods of marked sinoatrial bradycardia (a frequency lower than 90/min) are quite usual in newborn premature infants according to Church et al (26) and Philips et al (101) Välimäki agrees to this but he found periods of bradycardia to occur in term infants also (135)

Short episodes of paroxysmal ectopic tachycardia have been observed in long-term ECG recordings of asymptomatic adults (50 51). Similar episodes of tachycardia have also been found in newborn infants (135, 138)

Cardiac arrhythmias When the accuracy of the measurement of intervals is increased by the use of a computer analysis, cardiac arrhythmias have been found in a high percentage of long-term ECG recordings of premature infants (83, 84, 85) Arrhythmias usually occur in term infants during the first two days of life. There is no relation to the infant's sex or birth weight according to Välimäki (132). Escape beats are the commonest arrhythmias found in term and premature infants. Usually the arrhythmias are asymptomatic. Supraventricular extrasystoles, wandering pacemaker ventricular premature beats and paroxysmal ectopic tachycardia have been seen fairly frequently in newborn infants (26, 83 132, 134)

Heart rate patterns in infants with RDS

In the neonatal heart rate (NHR) there are continuous fluctuations, which indicate an active control of the vegetative nervous system regarding the cardiovascular function (52, 71 74 75 89 152) At present there is much evidence from adult, infant and fetal studies which supports the idea that a decrease in the heart rate indicates a suppression of the neurocirculatory control (1 106)

A clinical observation of infants with RDS have revealed that the heart rate tends to became fixed, i.e. the variation disappears (132, 139) Rudolph et al found a fixed heart rate in half of the RDS infants during the course of the disease (107). They suggest that the fixed heart rate is due to dysfunction of the medullary centres. Desmond et al (35) describe the presence of neurologic signs and depressed reflex activity during the dyspneic phase of RDS.

A fixed heart rate has been detected also in a high percentage of premature infants without RDS (132) Urbach et al (128) found a poor prognosis for the RDS infants who had a fixed heart rate

Vallbona et al. (137) observed the heart rate of decerebrated patients and found that there were prominent periodic waves of acceleration of the heart rate followed by a rebound deceleration. If there was a disconnection between the cardiac pacemaker and the cardiac regulatory centres a fixed heart rate was found.

In his preliminary investigation Välimäki (132) studied 10 RDS infants using a computer analysis which has a sufficient accuracy of measurement.

PRESENT INVESTIGATION

DESIGN OF THE METHOD

The present off line technique was designed to investigate if it would be medically and economically feasible to computerize the monitoring of the heart rate in an intensive care neonatal ward. A block diagram of the system is presented in Fig. 1.

The apparatus consists of a small recorder a special-purpose analyser (Electrocardiocorder Electrocardioscanner) and a digital computer. The present computer equipment consists of a PDP-8/L mini computer with 4 kwords of core memory an ASR 35 teletype, a high speed paper tape reader a clock oscillator with a frequency up to 20 kHz and three pulse input channels.

SIGNAL ACQUISITION AND ANALYSIS

Equipment for recording

In this investigation a mini tape-recorder Electrocardiocorder Model 330 (Avionics, Calif., USA) was used to record the ECG on a magnetic tape. However it may be used to record other signals similar in voltage and with a frequency up to 100 cycles sec. The rate of speed of the tape is 0.31 cm/s, allowing a full 8 hours of recording. The ECG signal is simultaneously recorded on two tracks of the magnetic tape. One is an amplitude modulated ECG pattern. The other is a sharp saw-tooth trigger pulse derived from the R waves of the ECG.

The purpose of this arrangement is that the trigger signal will adjust the QRS complex of the synchronous pattern recording in the middle of the display of the playback unit, Electrocardioscanner. The capacity of the power supply is for a continuous recording up to 8 hours. A repetitive one-millivolt pulse, with a frequency of 1 Hz, was obtained by means of the One-Millivolt Calibrator (Avionics) in order to calibrate the system.

Recording technique

Newborn infants are by no means ideal objects for an ECG recording because of their vigorous activity. Many of the sick infants need many kinds of nursing procedures like suction and respirator therapy. Thus it is not easy to get a noise-free recording of the ECG signal. All the classic disturbing factors, the alternating current noise, muscle potentials and wandering of the baseline must be eliminated.

Our electrodes, specially made for neonates, were of silver. They were square, 1.3 mm × 1.3 mm, and punched with holes to ensure a better contact.

The best electrode jelly proved to be the Trucon Electrode Paste (Electrodyne Westwood, Mass.). The skin was cleaned with an alcohol solution, rubbed until

heart can meet increased requirements only by increasing the heart rate.

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In his preliminary investigation Välimäki (132) studied 10 RDS infants using a computer analysis which has a sufficient accuracy of measurement.

In the present investigation the technically best part of the registration was chosen and then fed into the computer. The whole registration was visually checked and the aim was to select a representative segment from it. The segments with ectopic arrhythmias were rejected for the computer analysis.

COMPUTING TECHNIQUE

Description of the program

The trigger pulse originally recorded on the tape was used as the input for the analysis. The trigger pulse was adjusted for the computer pulse channel by an accessory amplifier. The trigger pulses were fed into the computer during the 60 times real-time-playback under oscilloscope control.

Calibration (Fig. 2). The calibration was carried out by measuring the time for 120 calibration intervals sampled from the initial 10-minute calibration period at the beginning of each recording.

The external calibration coefficient for normalizing the Electrocardioscanner output was computed and printed on the teleprinter. The internal calibration coefficient was estimated to convert the interval measurements to real-time intervals expressed in milliseconds.

For the R R interval analysis 520 successive R R intervals were measured, converted to real time values and stored in the core memory. An interval greater than 2048 msec as well as some errors detected by hardware caused an error condition and aborted the analysis. The computer also searched for noise pulses splitting the actual R R intervals. If a noise pulse was detected the splitted interval was regenerated by adding the two erroneous intervals and the remaining array was packed one location forwards. 10 such corrections were allowed for one analysis. The number of corrections was always printed out. This error correction subroutine was optional (Fig. 3).

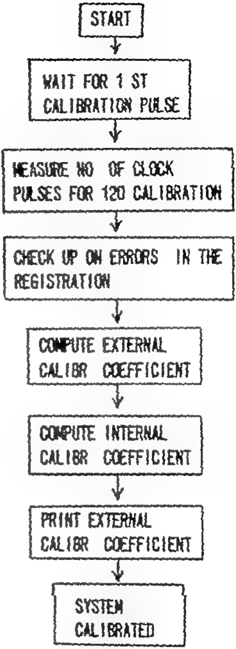

Fig. 2. Calibration program.

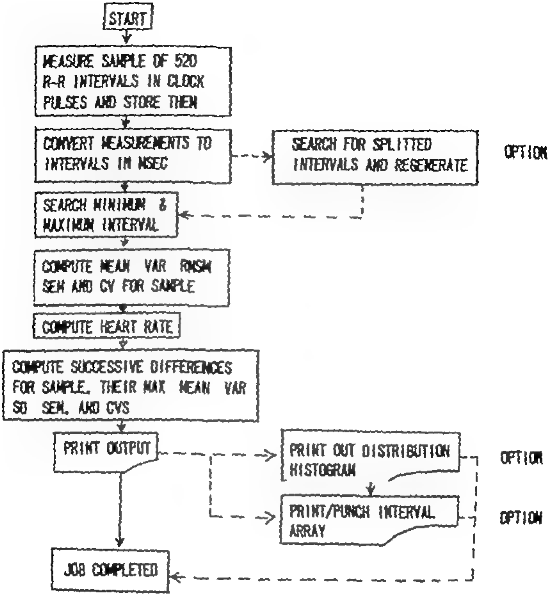

Fig. 2. Interval analysis program.

ECG INTERVAL ANALYSIS

RDS INFANT

Corrections	0000	
Heart rate interval	+ 144	/min
Mean	+ 416	ms
Min	+ 403	ms
Max	+ 431	ms
Variance	+ 27.2	ms
SD (RMSM)	+ 5.2	ms
SEM	+ 0.2	ms
CV	+ 1.3	%

Successive differences

Mean	+ 4.83	ms
Max.	+ 16 00	ms
Variance	+ 12.86	ms
SD	+ 3.74	ms
SEM	+ 0.17	ms
RMSSD	+ 8.10	ms
CVS	+ 1.74	%
Skewness	+ 0.14	
Kurtosis	+ 1.22	

HEALTHY INFANT

Corrections	0000	
Heart rate interval	+ 114	/min
Mean	+ 526	ms
Min	+ 433	ms
Max	+ 635	ms
V riance	+1615	ms
SD (RMSM)	+ 40.2	ms
SEM	+ 1.8	ms
CV	+ 7 6	/

Successive differences

Mean	+ 18.12	ms
Max.	+ 89 00	ms
Variance	+ 157.8	ms
SD	+ 12.56	ms
SEM	+ 0.56	ms
RMSSD	+ 19 65	ms
CVS	+ 2.74	%
Skewness	— 0.22	
Kurtosis	— 0.82	

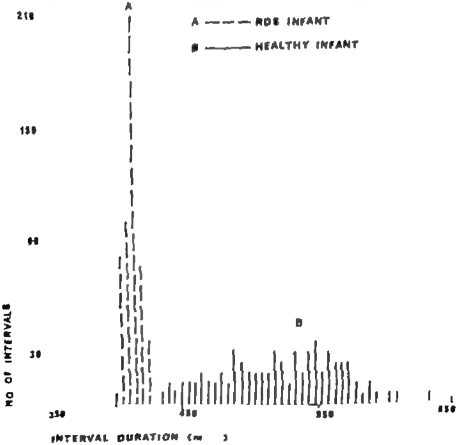

Fig. 4. ECG interval analysis of an RDS infant and healthy infant. A histogram of the mean R R interval f an RDS and healthy infant.

Mathematical expressions utilized in the computation

A total of 500 intervals were used for the final analysis. The computer identified the mean, minimum and maximum intervals and computed the mean, variance, root mean square of differences from the mean (RMSM) and the coefficient of variation for the RMSM (CV). The average heart rate was also calculated. The machine then extracted the successive interval differences and detected their maximum. On the basis of these differences the following parameters were computed: mean (MSD) variance, SD RMS-value of the successive differences (RMSSD) and the corresponding coefficient of variation (CVS). The skewness and kurtosis for the sample were estimated and the parameters were printed out (Fig. 4).

The overall variation, RMSM, was computed as the RMS value of differences from the mean.

$$\text{RMSM} = \sqrt{\frac{\sum (Y_i - \bar{Y})^2}{N}}$$

where Y_i is the i^{th} interval, $\bar{Y}$ is the mean of the intervals, and N is the total number of intervals.

Mean successive interval difference MSD,

$$\text{MSD} = \frac{\sum (Y_i - Y_{i+1})}{N-1}$$

RMSSD = Beat to-beat variation. This was defined as the RMS value of the differences between successive intervals

$$\text{RMSSD} = \sqrt{\frac{\sum (Y_i - Y_{i+1})^2}{N-1}}$$

where Y_i is the i^{th} interval in the sequence.

$$\text{SD}_{\text{MSD}} = \sqrt{\frac{\sum [(Y_i - Y_{i+1}) - \text{MSD}]^2}{N-1}}$$

Relative interval variation. The coefficient of variation was determined for the CV and CVS of the mean interval length ($\bar{X}$)

$$\text{CV}\ (\%) = \frac{\text{RMSM}}{\bar{X}}\ 100, \quad \text{CVS}\ (\%) = \frac{\text{RMSSD}}{\bar{X}}\ 100$$

Skewness. Skewness, third central moment of the distribution, is the degree of asymmetry or departure from symmetry of a distribution. If the frequency curve of a distribution has a longer tail to the right of the central maximum than to the left the distribution is said to be skewed to the right or to have a positive skewness. If the reverse is true, it is said to be skewed to the left or to have a negative skewness (113).

Kurtosis. Kurtosis is the degree of peakedness or the bimodality of a distribution, usually taken relative to a normal distribution. A distribution having relatively high peak such as the curve in Fig. 5 (a) is called leptokurtic, while the curve in Fig. 5 (b), which is flat topped, is called platykurtic. The normal distribution in Fig. 5 (c), which is not very peaked or very flat topped, is called mesokurtic.
In this study the kurtosis was said to be zero if it was mesokurtic, positive if it was leptokurtic and negative if it was platykurtic (113).

Histogram of the R R intervals. There was an option in the program to print a nonsequential distribution histogram for the 500 intervals. Each column corresponded to 5 msec and each asterisk to 6 intervals. The number of intervals falling out of range was also printed out. (Fig. 4.)

Serial correlogram. (Fig. 6) For validation and further analysis the whole interval array could be printed out and/or punched on an 8 channel paper tape. This tape output was used to compute a serial correlogram for the 500 intervals with a lag value up to 50. This correlogram program could not be loaded simultaneously with the actual interval analysis program (132).

Discrimination analysis. In the discrimination analysis was used the MAHALANOBIS DISTANCE analysis (77).

Index of merit. The reliability of this system to predict the development of RDS was determined by calculating the frequencies of correct positive and negative cases. The index of merit of the method was calculated as sum of the frequencies (in percentages) *minus 100.* Thus the maximum of this index is 100 %. (47).

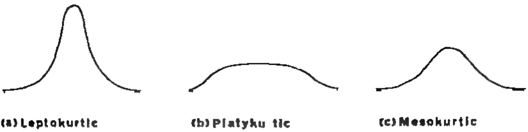

Fig. 5. Kurtosis.

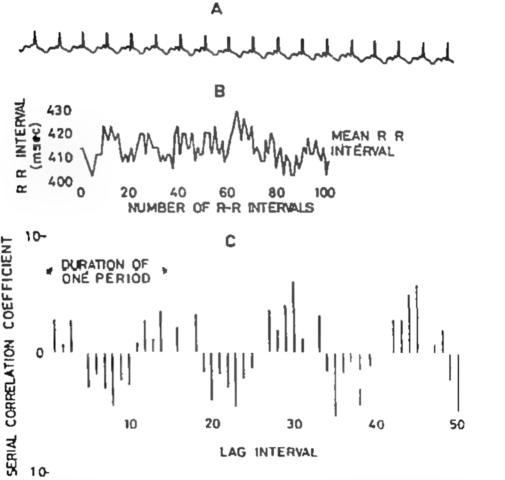

Fig. 6. A. ECG record of an RDS infant. Precordial bipola (C_3—C_{10}) lead. B. Sequential interval histogram of 100 successive R—R intervals from the record above. C. Serial correlogram computed for 500 R—R intervals from the data above. Note periodic variation with duration of one period of 13 intervals.

PATTERNS OF NEONATAL HEART RATE IN LONG TERM RECORDINGS

MATERIAL

The material consisted of 97 newborn infants, of which [illegible] were born at term (more than 266 days). There were 34 infants weighing over 2500 g. The subjects were divided into four groups: 1) normal infants, 2) infants whose mothers had received isoxsuprine during the labour 3) children who had a clinical syndrome of decerebration and 4) infants who developed RDS

Normal group

The group contained [illegible] neonates, of whom 16 were admitted because of prematurity and 4 because of hyperbilirubinemia to the neonatal ward of the Children s Hospital. The other 8 infants were in the nursery for healthy neonates. None of these infants had RDS but 3 of them had minor breathing difficulties the first day after birth (Table 10). The average birth weight was 2495 g (range 1220—4000 g) and the mean gestational age 252 days (range 206—280 days) (Table 3 4).

Isoxsuprine group

Isoxsuprine was given to the mother a) to prevent premature labour (116) b) to prevent development of RDS in the infant (63).

In this group all 10 infants were prematures (gestational age under 266 days) The birth weights of these infants were smaller than those in the other groups, on the average 1853 g (range 1330—2680 g) (Table 4) and the mean gestational age was 233 days (range 208—265 days) (Table 3) All of these infants were in good condition inspite of their prematurity In some of them the breathing was at first accelerated, but none of them developed RDS.

On the average about 153 mg of isoxsuprine was given during the labour The mean duration of the infusion was 24.5 hr The registration in this group was done during the first three days of life, because the purpose of this study was to find the possible influence of the drugs given to the mother on the heart rate of the infants. In four cases the registration was made for the first five days.

Decerebrated children

This group consisted of 4 children of whom one was decerebrated just after the delivery (the diagnosis was porencephaly). The age of another was one month and the diagnosis was: Reaction toxica ex usu sulfonamides. The two other children were 7 and [illegible] years old and were in the hospital because of car accidents. During the observation period

all of the children were »decerebrated (group DC») on the basis of EEG and clinical findings. The EEG was isoelectric and the patients were on a respirator without spontaneous breathing. They did not move at all and all of them died a little afterwards.

RDS group

The series of RDS infants included 55 patients, who shortly after birth started to present respiratory difficulties. Most of them had difficulty in initiating normal respiration and therefore they needed neonatal intensive care.

Criteria for the diagnosis of RDS

The clinical diagnosis of respiratory distress was based on the observation of the following criteria.

1. Respiration rate greater than 60/min or apnea.
2. Chest retraction.
3. Expiratory grunting.
4. Cyanosis inspite of oxygen administration.
5. Radiological findings (Reticulogranular infiltration throughout the lungs. An air bronchogram).

The average birth weight was 2200 g (range 790—3670 g) and the mean gestational age 231 days (range 182—280 days).

Only five of the infants were older than 38 weeks gestationally (over 266 days). During the pregnancy there were several complications, especially in the group of RDS infants. They have been listed in *Table 2*.

Nine of these infants were delivered by caesarean section and 5 of the mothers had diabetes mellitus. Five infants had asphyxia during the labour. There were three twins in the group of normal infants, five in the second group, and four in the isoxsuprine group. Two of the infants had placenta praevia, both belonged to the RDS group.

There were remarkable variations in the birth weights and gestational ages in the material (Table 3, 4).

The material was divided into four subgroups according to the birth weight (Table 4). This seemed justifiable considering the RDS risk of the infants and for comparing these groups with the main groups. A birth weight of 1250 g corresponds on the average to 29 gestational weeks and 2000 g to 33 weeks.

Table 2. Complications during the pregnancy.

	Normal	RDS	Isox suprine
Abortus imminens	6	10	10
Abnormal presentation	1	6	—
Caesarean section	2	9	—
Diabetes matris	—	5	—
Toxemia matris	3	5	1
Twins	3	5	4
Placenta praevia	—	2	—
Epilepsia matris	—	1	—
Hepatogestosis matris	—	1	—
Foetal asphyxia	2	5	—
Hydramnion	—	3	—
Administration of isoxsuprine to mother during the labour	—	3	10
Hypertensio matris	3	3	2

Table 3. Classification of the infants on the basis of their gestational age.

Gestational age (days)	(weeks)	Normal No. of cases	%	RDS No. of cases	%	Isoxsuprine No. of cases	%
Total		*28*		*55*		*10*	
Under 203	29	1	3.6	7	12.7	0	0
203—231	29—33	2	7.1	21	38.2	7	70
232—266	33—38	15	53.6	22	40.0	3	30
Over 266	over 38	10	35.7	5	9.1	—	
Mean gestational age (range)		[illegible]32 days (206—280)		231 days (182—280)		233 days (203—[illegible]65)	

Table 4. Classification of the infants on th basis of birth weights

Birth weight (g)	Normal No. of cases	%	RDS No. of cases	%	Isoxsuprine No. of cases	%
Under 1250	1	3.6	7	12.7	0	0
1250—2000	8	28.6	17	30.9	7	70
2000—2500	5	17.8	[illegible]	21.8	2	20
over 2500	14	50.0	19	34.6	1	10
Mean birth weight (range)	2495 g (1220—4000)		2200 g (790—3870)		1852 g (1330—2690)	

Classification of RDS infants groups I II III on the basis of the severity of the syndrome

In this investigation the infants were divided into three clinical groups I, II, and III (Table 5) The classification was based on the same clinical parameters we used when considering the severity of the RDS The infants were examined every day and the severity of the RDS was estimated. The final classification was made on the basis of the foll wing peri pheral cyanosis, sternal and intercostal retractions, respiration ate th influence of the ventilation on the colour of the infant and pulmonary auscultation (Table 6).

To quantify the severity of the disease, the following score was designed for the most severe symptoms the infant scored 3 points, for moderate symptoms 2 and for very slight symptoms 1 point. The system proved to be satisfactory in the final estimation of the disease. The in fants who scored 0—5 points belonged to the first group, to the second group the infants who got 6—10 points and the rest to group III.

Table 5. Clinical classification of the infants.

Score	Group I (0—5)	Group II (6—10)	Group III (11—15)	Total RDS infants
Number of cases	17	22	16	55
Mean birth weight	2076 g	2576 g	1815 g	2200 g
Mean gestational age	229 days	241 days	220 days	231 days

Table 6. Symptoms in the clinical classification f the RDS infants.

	Cyanosis	Intercostal retraction	Rate of breathing	Influence of ventilation on cyanosis	Pulmonary auscultation
Group I	Slight peripheral cyanosis	Slight retraction	60—80/min	No cyanosis, reasonable colour for a long time after the ven tilation	Good air entry to the lungs
Group II	Stationary moderate peripheral cyanosis	Moderate difficulties in breathing and retraction	80—100/min or infant in need of respiratory therapy or therapy with CPAP	Respiratory therapy repeated, assisted ven-tilation to keep off cyanosis	Air entry poor with spontaneous breathing much whirring and fine rales heard
Group III	Stationary grey-blue cyanosis also on respirator therapy	Heavy retrac-tions and difficulties in breathing Paradoxal breathing	Over 100/min or respiratory therapy	Cyanosis inspite of artificial ventilation	Air entry poor also with artificial ventilation. Spontaneous breathing super ficial breathing sounds weak.

Radiological classification of RDS infants (Table 7 8, 9)

On all the 55 infants a chest X ray was done the first day after birth, usually during the first hours. Dr E. Mäkinen, M.Sc., M.D Docent of Paediatric Radiology divided the infants on the basis of the severity of the chest X-ray findings into five categories without knowing the clinical history of the infants. He used five class, where the infants in the first had only slight changes from the normal and those in the fifth had the worst changes (Table 7) If the radiological classification is compared to the clinical one, it can be seen that they correspond quite well with one another (Table 9) The clinical group I was near the radiological classes 1 and 2, the clinical group II corresponded to the radiological classes 3 and 4, and the worst radiological category was near the clinical group III.

T ble 9 Radiological classification compared to the clinical on

	Radiological class				
Clinical group	1	2	3	4	5
Group I	5	7	2	3	—
Group II	—	7	8	[illegible]	2
Group III	—	2	2	8	5
Total	5	16	12	15	7

Table 7 Criteria in the radiological classification of th RDS infants.

Class 1. Slight granular infiltration due to slight peribronchial atelectasis, most of it in the central part of the lung field.

Class 2. Increased atelectasis and diffuse air bronchogram» findings. The peripheric part of the lungs still normal.

Class 3. In addition a pattern of alveolar opacification in the air bronchogram. Confluent opacification and dense reticular pattern make the borders of the diaphragm unclear in the central part of the lungs.

Class 4. Reticulogranular pattern involving the whole rea of the lungs. The borders of the heart are unsharp. The atelectasis in the basal part has increased.

Class 5. Lungs quite airless, an »air bronchogram is no longer seen. Impossible to distinguish the borders of the heart and the diaphragm.

Tabl 8 Radiological classification and birth weight in th RDS group.

	Radiological class									
Birth weight	1	(%)	2	(%)	3	(%)	4	(%)	5	(%)
Under 1250 g	—		1		1		1		4	
1250—2000 g	2		2		2		7		3	
Over 2000 g	3		13		9		7		—	
Number of infants	5	(9 1)	[illegible]	(29 1)	[illegible]	(21 8)	15	(27.3)	7	(12.7)

RDS subgroups

The respiratory distress syndrome included many kinds of infants. The history of the pregnancy as well as the etiology of the syndrome vary (Table 2). During the first day of life the RDS infants are subjected to many procedures, like an exchange transfusion, many of them are intubated and are on respirator therapy (Table 10). Then, in addition to the respiratory symptoms, there are many other reasons and procedures, which can influence the heart rate of the infants, and in this study the RDS infants are divided into six subgroups in order to find the possible differences reflected in these factors (Table 11).

T ble 10 Variables fter the delivery in the normal, the RDS and the isoxsupri group.

Variables	Normal	RDS	Isox suprine
Number of infants	29	55	10
Apgar scores/min	7.2	6.3	6.8
S-calcium mmol/l	1.9	1.9	2.0
P tplast (protrombin concentration)	0.22	0.18	0.19
Incubator therapy	19	53	10
Nasotracheal intubation	—	41	1
Respirator therapy	—	40	—
Exchange transfusion	4	16	2
Pneumothorax	—	4	—
Expired	—	11	—

Expired infants

A total of 8 infants succumbed (14.6) during the period of study. During the neonatal period three more infants died. Of these infants 8 were boys and 3 girls. The mean birth weight was 1729 g and the mean gestational age 221 days (Table 11). The respiration rate was significantly slower in the group of infants that expired (group Ex) compared to the group which included the other 44 RDS infants (group NonEx). All of these succumbed infants were intubated from the first day and were treated with respirator or CPAP therapy. All of them had hyaline membranes in the lungs seen in autopsies.

RDS infants treated with an exchange transfusion

16 infants belonged to this group. The indication for the exchange was hyper bilirubinemia. The amount of exchanged blood was °0 ° of the weight of the infant. Eight of the infants were boys and eight girls, the average birth weight was 1917 g and the average gestational age 220 days (Table 11). There were no significant differences between this group (group Ict) and the group of nonicteric RDS infants (group NonIct») in the respiration rates, in the acid-base balance, in the oxygen concentration used in the treatment.

The infants whose mothers h d toxemia during the pregnancy

Six of the RDS infants belonged to the group (group T) in which the mothers had toxemia during the pregnancy. Three of these infants were boys and three girls, the mean birth weight was 1715 g and the mean gestational age 224 days. Three of these infants succumbed but only one during the period of study. Two of the infants also had congenital heart disease (CHD). The birth we ght of these was 880 and 900 g respecti ely. The CHD was no doubt in addition to the RDS one of the causes of death (T ble 11).

There was n difference between groups T and NonT n the rate of respiration

in the oxygen concentration used in the treatment or in the acid-base balance.

Infants delivered by caesarean section

Nine of the 55 RDS infants were delivered by caesarean section (group CS), the others were born spontaneously (group NonCS). The indications for the caesarean section were maternal diabetes mellitus in 4 cases, placenta praevia in 2 cases, fetal asphyxia in 2 cases due to complications with the umbilical cord and suspected ablatio placentae in 1 case. The average birth weight was 3012 g in group CS and the mean gestational age 246 days (Table 11).

During the first day of life the respiration rate was significantly higher in group CS than in group NonCS . There was no difference between these groups in the acid-base balance, the oxygen concentration used in the treatment or in the chest X ray findings.

Infants born to diabetic mothers

In the RDS group there were five infants (group D) whose mothers had diabetes mellitus. Four of these infants were delivered by caesarean section done selectively in the 36th week because of the diabetes. Two of them were girls and three boys. The average birth weight was 3142 g and the average gestational age 241 days. There was no significant difference between group D and the other RDS infants (group NonD) in the respiration rates, except during the first day when the mean respiration rate was 92 in group D and [illegible] in group NonD . The chest X ray findings did not differ in either group. The oxygen concentration they breathed, and the acid base balance were also quite similar in the two groups.

Infants developing pneumothorax

In the RDS group there were 41 infants, who were intubated and treated with a respirator or with the CPAP system. In four of these infants pneumothorax developed during the treatment. Two of these died. The average birth weight in this group (group Pn) was 2560 g and the mean gestational age 246 days.

T ble 11 RDS subgroups.

(No f infants)	Birth weight (g)	Range	Gestational age (days)	Range	Clinical group 1	2	3	Radiol. classes 1	2	3	4	5	Sex distribution male/female (No. of infants)
					(No. of infants)			(No. of infants)					
1) Expired infa ts (11) group EX	1729	(880—3670)	221	(182—280)	1	2	8		2	2	3	5	8/3
2) Icteric infants (16) group Ict	1917	(790—2680)	220	(188—256)	5	7	4		4	6	5	1	8/8
3) Infants born to toxemic mothers (6) group T	1718	(880—3000)	224	(183—270)	2	4		1	2	1	1	1	3/3
4) Infants delivered by caesarean section (9) group CS	3012	(2430—3670)	248	(231—280)	2	6	1		3	4	2		5/4
5) Infants born to diabetic mothers (5) group D	3142	(2400—3830)	241	(231—251)	1	4			2	3			3/2
6) Infants who had pneumothorax (4) group Pn	2560	(1840—3050)	246	(227—270)		2	2		2		2		3/1
Total No. of RDS infants (35)	2200	(790—3670)	231	(182—280)	17	22	16	5	16	[illegible]	16	7	33/20

CLINICAL AND LABORATORY PROCEDURES

Physical examination of the infants

All the subjects were physically examined by the author every day during the observation period.

ECG recording

The ECG recordings were made from the first to the fifth day after birth. The first recording was made when the infant was only a *few* hours old and the next registrations at 24-hour intervals during the following 5 days. A total number of registration was in the normal group 134, in the RDS group 432 and in the isoxsuprine group 38.

Usually the registrations were made in the morning. The preparation of the skin, the mounting of the electrodes, and the recording technique have been described on page 15. Electrocardiocorder Model 350 A was utilized for the recording, and two or three electrodes were used as a bipolar precordial lead. At the beginning of each registration, a calibration pulse with a frequency of 1 Hz was recorded for 10 minutes. Each recording was made by the author himself. During the registration an effort was made to keep the infant quiet and all nursing procedures were avoided. The registration time was 30 minutes and the clinical condition (crying, restlessness) and possible therapeutic measures were documented in a diary. The analysis of the tape recordings was visually performed by means of Electrocardioscanner Model 460 described on page 16. If there were arrhythmias or noisy segments in the registration, it could not be analyzed with the computer and another better recording was chosen from the tape.

Laboratory investigation

In the normal group only routine chemical examinations were performed: blood sugar (Dextrostix® Ames) serum-calcium, tromboplast and, if necessary, the acid-base balance (from 20 infants). A chest X-ray was done on 17 infants in this group.

In the RDS group the serum-calcium, the blood glucose and the acid-base balance were estimated several times a day. A chest X ray was done the first day and after that if considered necessary. A total of 152 chest X rays were done on the RDS-infants. Also blood counts and the tromboplast were determined. In 10 cases the total protein from the blood of the umbilical cord was also examined.

In the isoxsuprine group the same diagnostic procedures were carried out as on the RDS infants, because all of them were prematures.

Parameters in the various forms of therapy

The treatment followed the usual principles of the treatment of RDS (6, 96, 98, 104, 111, 118, 120). When necessary the infant was intubated and was ventilated with a respirator (Loosco® G. L. Loosco, Amsterdam). Intermittent positive pressure respiration (= IPPR) or a continuous positive airway pressure (CPAP) was used (44). The following parameters for respiratory failure were used to justify the nasotracheal intubation.

a) Rising pCO_2 (over 6 kPa) and cyanosis unrelieved by a high concentration of inspired oxygen.

b) Fall in respiratory rate or periods of apnea or a tachypnea (over 100/min) and increasing acidosis, i.e. falling pH partly respiratory due to the high pCO partly metabolic, due to hypoxemia.

Table 12. The ages of the infants when the registrations were made.

Number of registration	Normal		RDS		Isoxsuprine	
	Days	Hours	Days	Hours	Days	Hours
1.	—	10	—	8	—	5
2.	1	10	1	5	1	2
3.	2	10	2	5	2	2
4.	3	11	3	5	3	5
5.	4	10	4	8	4	5

c) Evidence of peripheral circulatory failure or bradycardia, the positive pressure in the respirator was at first 15—20 cm H_2O and a mild positive end-expiratory pressure (2—3 cm H_2O) was also used. If this was not satisfactory the pressure was increased to 25—30 cm H_2O in the respirator. If the CPAP only was used, the positive pressure was 8 cm H_2O in the nasotracheal tube. The infants were in incubators when examined (AIR-SHIELD® Osborne, USA). The oxygen was monitored with oxygen meters (Beckman® Fullerton, Calif. or Mira® Los Angeles, Calif.). If the infant was intubated the oxygen was measured from the air going to the lungs of the infants.

The *respiration rate* was significantly lower in the normal and the isoxsuprine group than in the RDS group ($p < 0.001$). In the RDS group 41 infants were on a respirator or CPAP therapy and the rate of ventilation was usually 55 per minute in the Loosco® respirator.

On an average the rate of respiration was 48 cycles/min in the normal, 66 in the RDS and 50 in the isoxsuprine group (Fig. 9).

Oxygen therapy was only used sometimes in the treatment of the normal and the isoxsuprine group, but in the RDS group oxygen administration was one of the basic measures of treatment (Fig. 9).

Acid-base balance. pH, pCO_2, HCO_3 were measured on an average every 6—8 hours (night and day) during the first day and after that 1—2 times per day or when it was considered necessary. If the infants had metabolic acidosis, they were given $NaHCO_3$ or THAM (Trishydroxymethyl amino-methane) intravenously to keep the $pH > 7.25$. $NaHCO_3$ was not given more than 10 mEq/kg/4 hrs.

Just before or after the ECG recording the acid-base balance was determined for the RDS infants, but not for every normal infant. There was only during the first day a little difference in the average pH 7.29 ± 0.06 in the normal, 7.24 ± 0.08 in the RDS and 7.31 ± 0.06 in the isoxsuprine group. After that there was no difference because of the $NaHCO_3$ given if the infants had acidosis.

Intravenous fluid therapy. All of the RDS infants were fed through a umbilical catheter (venous or arterial) for the first two or three days. During the first day of life 60 ml/kg/day of 10 % glucose was given intravenously and after that gradually more, 100 ml/kg/day by the fourth day. From the second day on the infant was also given NaCL.

If the infant had edematous extremities it was given furosemid (Furesis® Leiras Oy), usually 1—3 mg day

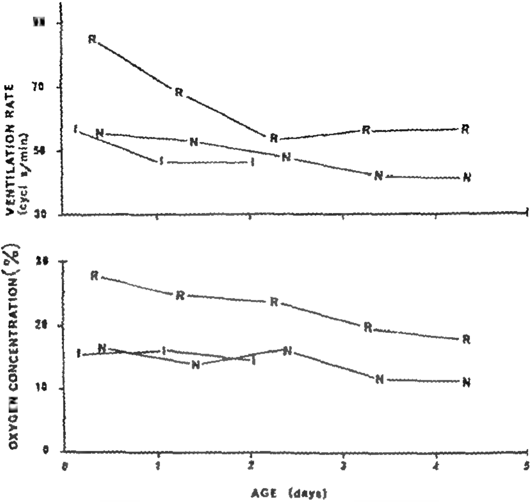

Fig. 8 Mean respiration and/or mean ventilation rate with the normal (N) the RDS (R) and the isoxsuprine (I) infants (Above). Mean oxygen concentration (%) used in the treatment of the normal (N) the RDS (R) and the isoxsuprine (I) infants.

RESULTS

HEART RATE PATTERNS

Mean heart rate in the normal, the RDS and the isoxsuprine group

The mean heart rates for the normal, the RDS and the isoxsuprine group during the observation period are presented in *Fig. 10*. There were *significant* ($p < 0.001$) differences in the mean heart rate between the normal (on an average 133 beats/min) and the RDS group (on an average 140 beats/min). The standard deviation was practically equal in both groups. In the normal group the mean heart rate was remarkably even during the whole observation period (Table 14, Fig. 10) and in the RDS group there were also very few changes during the first five days of life. There were no significant differences between the boys and the girls. Th mean *heart rate* was not *significantly different* between the isoxsuprine group and the normal group, but the differences between the isoxsuprine group and the RDS group were significant ($p < 0.001$) during the first three days (Fig. 10). The mean heart rate f the healthy (9) infants weighing ≤ 2000 g was (139 beats/min) significantly greater than that of the healthy (19) infants weighing > 2000 g (130 beats/min). In the RDS group there was no clear relation between the mean heart rate and the weight.

Mean, minimum and maximum R-R interval

The mean R R interval was significantly longer ($p < 0.001$) in the normal than in the RDS group (Table 14, Fig. 10), and it was also in the isoxsuprine group significantly longer than in the RDS group.

There were no significant differences in the minimum R R interval in the normal (393 msec ± 38) in the RDS (390 msec ± 47) or in the isoxsuprine group (406 msec ± 56) (*The corresponding* heart rates were 152 ± 15, 154 ± 19, 148 ± 21 beats/min).

The average maximum R-R interval was significantly shorter ($p < 0.001$) in the RDS group than in the normal group. In the isoxsuprine group it was ($p < 0.001$) shorter than in the normal group but longer ($p < 0.001$) than in the RDS group during the first three days (Fig. 10). (The corresponding heart rates were. 109 ± 10 in the normal, 124 ± 16 in the RDS and 118 ± 17 in the isoxsuprine group.)

Overall heart rate variation, RMSM and CV

Between the normal and the RDS group there were significant differences in the RMSM (the mean overall variation) ($p < 0.001$). The RMSM was on the average 25.7 ± 13.8 msec in the normal group and

14.4 ± 7.4 msec in the RDS group. In the RDS group the RMSM showed a continuous tendency to increase. The corresponding values of the relative overall variation (CV) — 5.6 %, 3.4 % — also differed significantly ($p < 0.001$). The CV increased in both groups from the first to the fifth day of life (4.8 % to 6.2 % in the normal and 3.0 % to 4.1 % in the RDS group). The RMSM was significantly shorter in the normal group for the 9 infants weighing < 2000 g, than for the 19 larger infants (> 2000 g). In the RDS group the 23 infants weighing < 2000 g also had a shorter RMSM than the 32 larger ones. The differences were significant ($p < 0.001$) also between the healthy infants weighing < 2000 g and the RDS infants weighing > 2000 g (19 msec and 18 msec respectively). There were no clear differences between the RDS and the isoxsuprine group in the RMSM, but the differences between the normal and the isoxsuprine group in the RMSM were significant ($p < 0.001$) during the observation period (Table 14).

In the isoxsuprine group the CV was near the values in the RDS group but between the normal and the isoxsuprine group there were significant differences in the CV (Table 13).

Beat-to-beat variation, MSD RMSSD and CVS

Mean successive difference (MSD). The mean successive difference was significantly shorter ($p < 0.001$) in the RDS (10.2 ± 3.2 msec) than in the normal group (11.2 ± 6.0 msec).

In both groups the MSD decreased during the second day and after that it showed an increasing trend. The va i t ons in the RDS group of the MSD w very sl ght during the observatio n d (T bl Fig. 11). In the isoxsuprine group the MSD was greater than in the RDS group during the observation period, but the differences were very small (Table 15).

RMSSD. During the first day the RMSSD was 19 msec in the normal group and 12.9 msec in the RDS group, the difference was significant ($p < 0.001$), but during the second day the difference in RMSSD was not equally distinct (Table 15).

No difference could be found in the RMSM or RMSSD in relation to the sex. In the isoxsuprine group the RMSSD was significantly greater during the first two days but on the third day there was no difference.

In the normal group the CVS was greater than in the RDS group during the whole observation period with the exception of the second day.

T ble 13. CV (%) ± SD in the normal, the RDS and the isoxsuprine group during the first five days.

Day	Normal CV (%) ± SD (No. of infants)	RDS CV (%) ± SD (No. of infants)	Isoxsuprine CV (%) ± SD (No. of infants)
1	4.8 ± 2.8 (28)	3.0 ± 1.0 (35)	3.1 ± 0.9 (10)
2	5.2 ± 2.9 (28)	2.9 ± 1.1 (55)	3.2 ± 1.0 (10)
3	6.3 ± 2.7 (28)	3.2 ± 1.3 (52)	3.8 ± 1.2 (10)
4	5.4 ± 2.7 (8)	3.6 ± 1.7 (49)	2.9 ± 0.5 (4)
5	6 ± 1.6 (26)	4.1 ± 1.0 (47)	3.2 ± 1.7 (4)
T t l	5.6 ± 3	3.4 ± 1.2	3.4 ± 1.0

Tabl 14 Mean heart rate (beats/minut ± SD), (number of infants), mean R R interval (msec ± SD) and mean RMSM (msec ± SD) in the normal, the RDS and th isoxsuprine group during the first five days of life.

Day	Normal: Heart rat beats/ min ± SD (No of infants)	Normal: Mean R R interval msec ± SD	Normal: Mean RMSM msec ± SD	RDS: Heart rate beats/ min ± SD (No. of infants)	RDS: Mean R R interval msec ± SD	RDS: Mean RMSM msec ± SD	Isoxsuprine: Heart rate beats/ min ± SD (No. of infants)	Isoxsuprine: Mean R R interval msec ± SD	Isoxsuprine: Mean RMSM msec ± SD
1	133 ± 17 (28)	451 ± 52	22.9 ± 13.0	141 ± 14 (85)	429 ± 43	12.8 ± 5.4	128 ± 18 (10)	447 ± 46	13.7 ± 4.3
2.	132 ± 12 (28)	456 ± 43	24.1 ± 10.3	143 ± 15 (83)	428 ± 45	12.5 ± 8.7	135 ± 16 (10)	450 ± 56	14.2 ± 4.3
3.	134 ± 13 (28)	455 ± 44	20.1 ± 14.1	137 ± 15 (32)	442 ± 51	14.2 ± 7.1	133 ± 14 (10)	460 ± 48	17.3 ± 8.3
4.	134 ± 13 (28)	452 ± 42	24.7 ± 16.0	141 ± 16 (49)	432 ± 52	13.6 ± [illegible]	142 ± 34 (4)	432 ± 73	12.4 ± 1.3
5.	131 ± 13 (26)	461 ± 47	20.5 ± 8.5	139 ± 14 (47)	430 ± 44	17.6 ± 9.2	131 ± 21 (4)	469 ± 80	14.5 ± 6.3
Total	133 ± 14	457 ± 47	25.7 ± 13.8	140 ± 15	433 ± 47	14.4 ± 7.4	133 ± 16	453 ± 54	14.6 ± 4.0

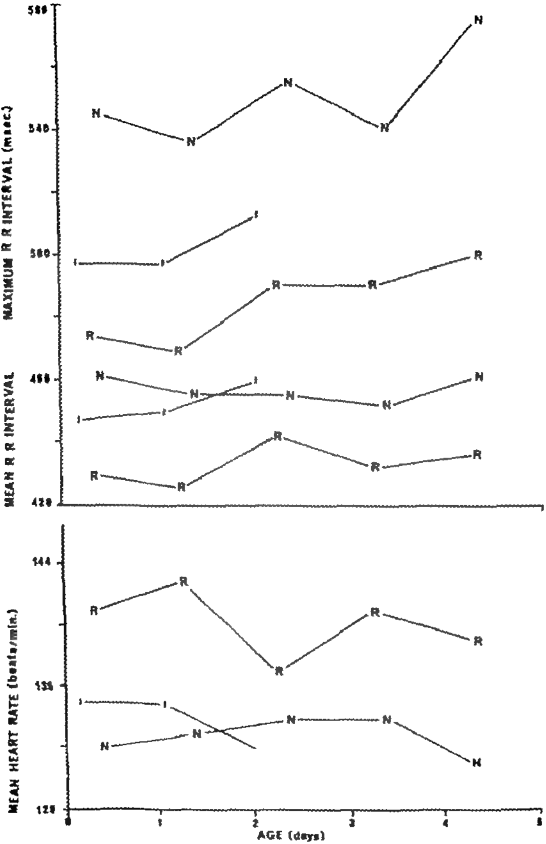

Fig. 10. Mean heart rate (b[illegible] m[illegible] me[illegible] R R [illegible]nter[illegible]al (msec) [illegible]nd maximum R R interval (msec) in the normal (N), th[illegible] [illegible] R[illegible] [illegible]nd the isoxsuprine (I) infants during the first [illegible] days of lif[illegible]

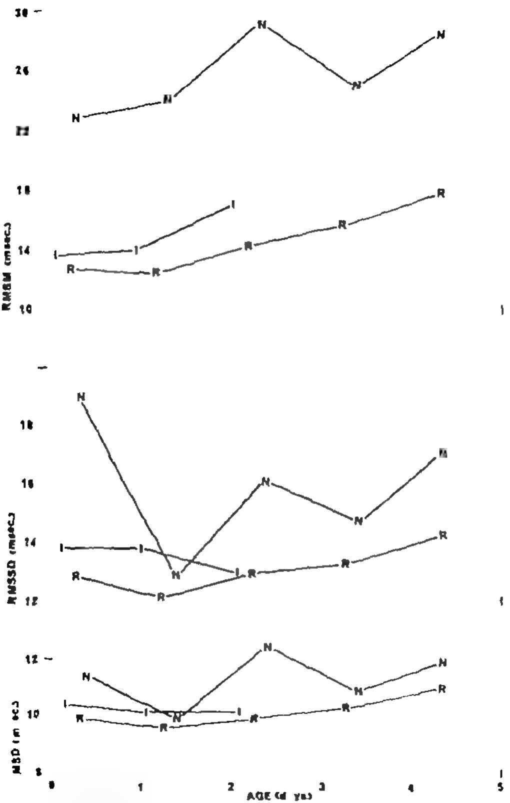

Fig. 11 Mean RMSM (msec) RMSSD (msec) and MSD (msec) in the normal (N), the RDS (R) and the isoxsuprine (I) group during the first five days of life.

Tabl 15 Mean MSD (msec ± SD), RMSSD (msec ±) and CVS (% ± SD) in the normal, the RDS and the isoxsuprine group

Day	Normal			RDS			Isoxsuprine		
	MSD msec ± SD (No of infants)	RMSSD msec ± SD	CVS % ± SD	MSD msec ± SD (No. of infants)	RMSSD msec ± SD	CVS ± SD	MSD msec ± SD (No. of infants)	RMSSD msec ± SD	CVS % ± SD
1	11 3 ± [illegible] ([illegible])	19 0 ± [illegible]	3.3 ± 1 7	9.9 ± 4.5 (85)	13.9 ± 4.5	3.0 ± 1 1	10.4 ± 3.3 (10)	13.9 ± 4.3	3.0 ± 0 9
	9 0 ± 3 0 (28)	12 9 ± 3 3	2 8 ± 1.0	9 6 ± 2.9 (55)	13.3 ± 3.7	3.9 ± 1 0	10.3 ± 2 5 (10)	12.9 ± 5.1	3.0 ± 0 9
3	12 3 ± 8 1 (28)	16 2 ± 10.5	3.5 ± 1.9	9.9 ± 2.9 (52)	13.0 ± 3.7	2.9 ± 0.9	10.1 ± 2.9 (10)	13.0 ± 2.6	2.8 ± 0.8
4	10 9 ± 3 5 (25)	14 8 ± 5.4	3.3 ± 1.3	10 3 ± 3.8 (49)	13.5 ± 4.5	3 1 ± 1 0	13 1 ± 1.3 (4)	16.7 ± 1.9	4.0 ± 1.1
5	11.9 ± 6 7 (26)	17 1 ± 8 1	3 7 ± 1.9	11.0 ± 3.3 (47)	14 3 ± 4.2	3.3 ± 1.0	11.4 ± 1.3 (4)	17.9 ± 5.4	3.9 ± 1 7
T tal	11.3 ± 6 0	15.1 ± 8.3	3.3 ± 1.8	10.3 ± 3.3	13.1 ± 4.2	3.0 ± 1.0	10.7 ± 2.8	14.3 ± 4.5	3 0 ± 1.0

T ble 16 Period variation (PV) in the ECG registrations in the normal, the RDS and the isoxsuprine group Incidence of periodic variation and duration of a period (sec).

	Periodic variation (PV)								
	Normal			RDS			Isoxsuprine		
	Incidence of PV		Duration of	Incidence of PV		Duration of	Incidence of PV		Duration of
	No. of registr / total registr	%	a period (sec)	No. of registr / total registr	%	a period (sec)	No. of registr / total registr	%	a period (sec)
1.	26/28	93	4.8 ± 0.9	84/85	98	3.9 ± 1.3	10	100	4.3 ± 1.3
2.	26/28	93	4 7 ± 1.3	53/55	96	4.1 ± 1 1	9	90	3.9 ± 0.5
3.	21/28	75	4.7 ± 1.5	50/52	96	4.3 ± 1 1	8	80	3.9 ± 0.4
4	17/28	61	5 5 ± 3.3	44/49	90	4.0 ± 1..	4	100	4.7 ± 0.7
5.	14/28	50	5 8 ± 3.8	42/47	79	3 8 ± 1 1	4	100	4.0 ± 0.8

Skewness

The mean skewness of the R–R interval distribution was positive in all groups. During the first three days the skewness decreased, but during the 4th and 5th days it increased in the normal and the RDS group (Fig. 12). The skewness was significantly bigger in the normal group ($p < 0.001$) during all other days except the second day than in the RDS group.

Kurtosis

Between the normal and the RDS group there were no clear differences in the kurtosis. During the last two days the kurtosis was greater in both groups than during the first three days. The values of the isoxsuprine group were also near the values of the other groups.

Periodic variation

A periodic variation was found the first day in the normal group in 23 (93 %) infants, in the RDS group in 54 (96 %) infants and in all the infants of the isoxsuprine group. During the observation period the incidence of this variation decreased gradually both in the normal and the RDS group (Table 16). The duration of the variation period was shorter in the RDS group than in the normal group (Fig. 13).

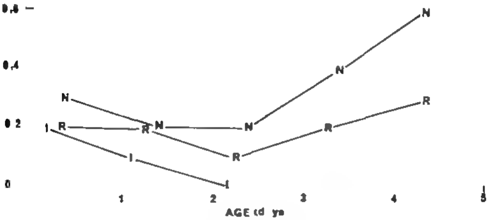

Fig. 12. Mean skewness of R R interval distribution in the normal (N), the RDS (R) and the isoxsuprine (I) group.

Discriminant analysis (Mahalanobis distance) between the normal and the RDS group

a) Discrimination function coefficient for the variables used

An analysis was made regarding which of the parameters used had the best discriminating power between the normal and the RDS group. On the first day the RMSM had the best value, but after that the RMSSD clearly had the greatest coefficient (Table 17).

b) Discriminant analysis (Mahalanobis distance) between the groups

To increase the power of discrimination between the normal and the RDS group

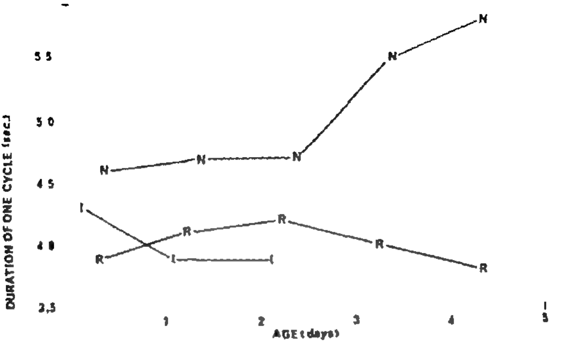

Fig. 13. Mean duration of one cycle of periodic variation (sec) in the serial correlogram of the normal (N), the RDS (R) and the isoxsuprine (I) infants.

Table 17. Discrimination function coefficient during the first five days between the RDS and the normal group.

Variables	1th day	2nd day	3rd day	4th day	5th day
Heart rate	0.1840	0.1889	0.4377	0.3651	0.1749
Variance	1.154	1.734	0.2750	0.7454	1.064
RMSM	2.464	2.810	1.481	1.811	2.503
MSD	1.371	1.793	17.01	8.797	3.310
RMSSD	1.480	4.675	20.33	10.67	6.850

the RMSM, RMSSD and the birth weight were utilized together as discriminators. It was studied how well the infants could be characterized normal or abnormal with this set of parameters. The whole period of five days was considered. Six of the RDS infants belonged to the normal group with this analysis, i.e. they were false negative cases. The average birth weight was 2363 g and the mean gest t onal age 236 days for these false ne t e nf n (In the total RDS group c esp di. l 2200 g and 231 days). Two of these infants belonged to the first clinical group and four to group II. None of them were from the worst clinical group. Two of the mothers of these infants had diabetes mellitus. Correspondingly 8 (21 /) of the normal 38 infants belonged to the RDS group according to this system, i.e. they were false positive cases. In the isoxsuprine group six infants belonged to the normal and four to the RDS group

c) Discriminant analysis of RDS group day by day using the RMSM and RMSSD as discriminators

The RDS group was analysed day by day and then only the RMSM and the RMSSD not the birth weight of the infants were used. With this system 12 (22 %) infants had been classified as belonging to the normal group during the first day (false negative cases) Six of these infants belonged to clinical group I and six to group II. Many of these false negative cases of the first day remained outside the RDS group also afterwards (Table 21 Fig 14).

During the first day there were 12 false negative infants, and six of them were false negative cases for the whole observation period. During the third and fourth days seven and during the fifth day eight of these 12 infants were false negative cases.

Table 18. Normal infants which belonged to the RDS group according to the discriminant analysis (false positive cases).

Infant	Birth weight	Gestational age	Gestation history	Diagnosis
1.N.	1600 g	234 days	Toxaemia, hypertensio matris	Prematurity Healthy infant
2 M	2150	241	Abnormal presentation	Prematurity Healthy infant
3 N.	1600	206	Abortus imminens	Prematurity Healthy infant
4.H.	2030	238	Twin	Prematurity Cong. heart disease
5 P	3110	270		Hyperbilirubinemia Acidosis post partum
6.H.	3420	280		Healthy infant
On an average	2328 g	246 days		

Table 19 Reclassification of the infants on the basis of the discriminant analysis using the RMSM RMSSD and the birth weight as discriminators

	From clinical groups	To normal group		To RDS group	
	No. of infants in the group	No. of infants	% of the group	No. of infants	% of the group
RDS group I	17	2	12	—	—
RDS group II	22	4	[illegible]	—	—
RDS group III	16	—	—	—	—
Total RDS group	55	6	11	—	—
Normal group	[illegible]	—	—	5	[illegible]
Isoxsuprine group	10	6	60	4	40

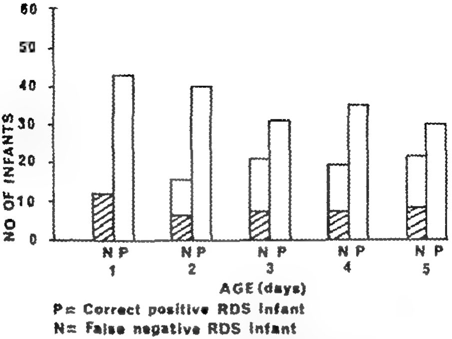

Fig. 14. Discriminant analysis of RDS infants. False negative (N) and correct positive cases (P). The ruled area in column N includes the number of RDS infants, persisting false negatives during the whole observation period.

T ble 20 Diagnosis of RSD on the basis f heart rate variations index of merit analysis.

	Correct positive		Correct negative		Index of merit of the method
Clinical group (No. of infants)	No. of infants	/	No. of infants	/	
RDS infants (55) Normal (28)	49/55	89	22/28	79	68
RDS infants (55) Normal (28) Isoxsupr (10)	49/55	89	28/38	74	63

Table 21 Reclassif cation f th RDS nfants day by day on the basis of the RMSM nd RMSSD during th first f ve days of life.

Day	■ of false negati cases	of total RSD group	No. of correct positive RDS cases	of total RDS group
1	1	22	43	78
2	15	27	40	73
3	1	40	31	60
4	14	9	33	71
5	1	36	30	64

Clinical RDS intergroups I, II and III

Mean heart rate. The RDS group was divided into three clinical subgroups (page 26). In group III the mean heart rate was significantly higher than in the other groups, except that in RDS group II during the second day of life. Between groups I and II there were significant differences in the mean heart rate only during the first two days. The heart rate showed a decreasing trend during the observation period in groups II and III (Table 24 Fig. 15).

— *RMSM* (overall heart rate variation) The RMSM was significantly smaller in group III than in the other (I and II) groups during the observation period ($p < 0\,0001$) The differences in RMSM between group III and the other groups increased all the time.

The differences in RMSM between groups I and II were small during the first five days (Table 25 Fig 16) All of the intergroup differences in CV were significant ($p < 0\,001$) (Table 22)

— *MSD* (mean successive difference) The MSD was significantly ($p < 0\,001$) lower in group III than in the other RDS groups. During the second day the differences in MSD between the groups were slight. After that the MSD began to decrease in group III and to increase in the other groups. The differences were significant ($p < 0\,001$) (Table 26).

— *RMSSD* (beat to-beat variation) The RMSSD in groups I, II and III are presented in Fig 15 and in Table 27 The figures for the RMSSD were quite similar to those for the MSD The RMSSD in group III differed significantly from the values of the other groups during the 1st, 3rd, 4th and 5th days ($p < 0.001$) respectively between all the intergroups. In the CV there were significant differences during the same days (Table 22) In group I and II the RMSSD increased after the second day but in group III it decreased.

Table 22 Relative overall variation (CV) and relative beat to-beat variation (CVS) in the clinical RDS group.

Day	Clinical RDS group I: CV ± SD (No. of infants)	II: CV % ± SD (No of infants)	III: CV ± SD (No of infants)	Clinical RDS group I: CVS ± SD (No. of infants)	II: CVS ± SD (No of infants)	III: CVS ± SD (No of infants)
1.	3 4 ± 1 0 (17)	3 0 ± 1 1 (22)	2 4 ± 0 7 (16)	3 2 ± 0 8 (17)	3 0 ± 1 1 (22)	[illegible]8 ± 1 2 (16)
2.	3 4 ± 1 0 (17)	3 0 ± 1 2 (22)	2 4 ± 0 7 (16)	2 9 ± 0 6 (17)	3 0 ± 1 1 (22)	3 0 ± 1 2 (16)
3.	3 7 ± 1 5 (17)	3 2 ± 1 3 (23)	2 4 ± 0 6 (13)	3 1 ± 0 6 (17)	2 9 ± 0 8 (22)	2 8 ± 1 3 (13)
4.	4 3 ± 1 5 (16)	3 8 ± 1 8 (22)	2 1 ± 0 7 (11)	3 5 ± 1 3 (16)	3 1 ± 0 7 (22)	3 ± 0 6 (11)
5.	4 1 ± 1 5 (16)	4 8 ± 2 4 (22)	2 8 ± 1 7 (9)	3 4 ± 0.7 (16)	3 6 ± 1 1 (22)	3 ± 6 (9)
Total	3 8 ± 1 3	3 5 ± 1 6	2 4 ± 0 9	3 2 ± 0 8	3 1 ± 1.0	2.5 ± 1 0

— *Assisted ventilation and heart rate patterns.* The RDS infants were divided into two categories on the basis of breathing infants with nasotracheal intubation and infants without intubation. Those who were intubated and ventilated had a significantly higher heart rate during the first two days ($p < 0.001$) but after that there were no differences between the categories. For the first two days in group II there was also a significantly higher heart rate in the intubated infants than in the infants breathing spontaneously. After that only four infants breathed spontaneously in this group and consequently the differences cannot be taken into account.

The RMSM was significantly ($p < 0.001$) lower for the intubated infants only during the first day and after that vice versa. (Table 25). During the first day the MSD and the RMSSD were lower for the infants who were ventilated artificially than for the spontaneously breathing infants. After the first day the MSD was again lower for the intubated infants.

— *Heart rate patterns in cyanotic infants.* One of the clinical scoring systems was to divide the RDS infants on the basis of the cyanosis of the skin into three categories. The most cyanotic infants were in category 3 and the infants who had only slight cyanosis were in category 1. In the basic heart rate were not seen any clear differences between these categories. In the RMSM and RMSSD there were no clear differences between the categories of cyanosis either.

Discriminant analysis of the RDS infants using the RMSM, RMSSD and the birth weight as discriminators

The RDS infants were replaced in the clinical groups on the basis of the RMSM, RMSSD and the birth weight observations for the whole five day period (Table 23).

Table 23. Discriminant analysis of the RDS infants using the RMSM, RMSSD and the birth weight as discriminators.

		Correct positive		Correct negative		Index of merit of the method
Clinical group	N of infants	No. of infants		No. of infants	%	
Group I	17	10/17	59	31/38	82	41
Group II	22	14/22	64	24/33	73	37
Group III	16	10/16	63	34/39	87	50

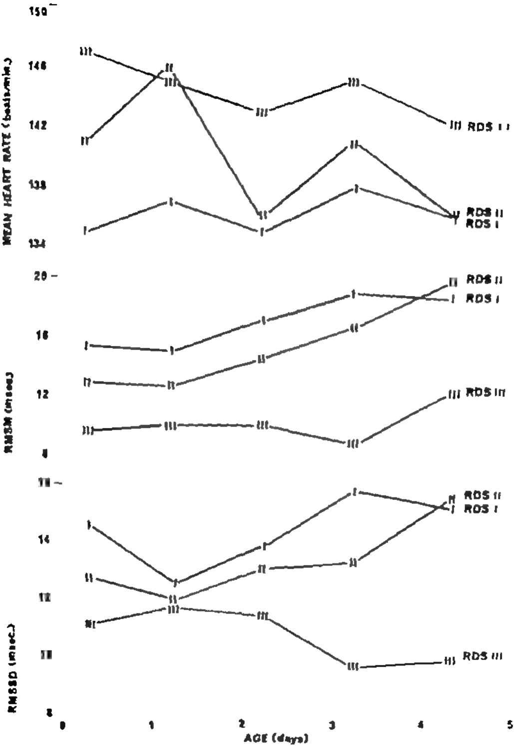

Fig. 18. Mean heart rate (beats/min), RMSM (msec) and RMSSD (msec) in RDS groups I II and III during the first five days of life.

Table 24 Mean heart rate in the infants of groups I, II and III (beats/minute) (Number of infants), in the intubated infants and in the infants who breathed spontaneously.

	RDS I			RDS II			RDS III		
	Total	Not intubated	Intubated	Total	Not intubated	Intubated	Total	Not intubated	Intubated
Day	Beats/ min ± SD (No. of infants)	Beats/ min ± SD (No. of infants)	Beats/ min ± SD (No. of infants)	Beats/ min ± SD (No. of infants)	Beats/ min ± SD (No. of infants)	Beats/ min ± SD (No. of infants)	Beats/ min ± SD (No. of infants)	Beats/ min ± SD (No. of infants)	Beats/ min ± SD (No. of infants)
1	136 ± 13 (17)	135 ± 13 (15)	140 ± 21 (2)	141 ± 13 (22)	138 ± 13 (12)	147 ± 12 (10)	147 ± 13 (16)	133 ± 4 (3)	150 ± 12 (13)
2	137 ± 14 (17)	137 ± 14 (14)	137 ± 14 (3)	146 ± 14 (22)	137 ± 13 (6)	149 ± 14 (16)	148 ± 17 (16)	0	148 ± 17 (16)
3	136 ± 15 (17)	135 ± 15 (14)	141 ± 17 (3)	138 ± 16 (22)	141 ± 9 (4)	134 ± 18 (18)	143 ± 14 (13)	0	143 ± 14 (13)
4	138 ± 14 (16)	137 ± 16 (13)	141 ± 8 (3)	141 ± 17 (23)	149 ± 6 (4)	140 ± 19 (18)	145 ± 14 (11)	0	145 ± 14 (11)
5	138 ± 14 (16)	137 ± 15 (13)	138 ± 9 (3)	136 ± 14 (22)	137 ± 15 (7)	135 ± 9 (15)	142 ± 10 (9)	0	142 ± 10 (9)
Total	137 ± 14	136 ± 14	139 ± 14	139 ± 16	140 ± 11	141 ± 14	144 ± 19		145 ± 14

Table 25 Mean RMSM (msec) for the infants in groups I, II and III for the intubated and spontaneously breathing infants in these groups.

Day	RDS I			RDS II			RDS III		
	Total msec ± SD (No. of infants)	Not intubated msec ± SD (No. of infants)	Intubated msec ± SD (No. of infants)	Total msec ± SD (No. of infants)	Not intubated msec ± SD (No. of infants)	Intubated msec ± SD (No. of infants)	Total msec ± SD (No. of infants)	Not intubated msec ± SD (No. of infants)	Intubated msec ± SD (No. of infants)
1.	18.5 ± 6.2 (17)	19.7 ± 8.7 (15)	14.0 ± 3.3 (2)	13.9 ± 8.1 (22)	14.4 ± 6.8 (12)	11.1 ± 1.5 (10)	9.8 ± 3.0 (16)	11.6 ± 3.0 (3)	9.4 ± 2.9 (13)
2.	15.0 ± 4.8 (17)	15.3 ± 5.1 (14)	14.3 ± 3.2 (4)	12.6 ± 7.3 (22)	11.3 ± 3.8 (7)	13.2 ± 8.2 (16)	10.1 ± 2.9 (16)	0	10.1 ± 2.8 (16)
3.	17.0 ± 8.2 (17)	17.8 ± 8.9 (14)	12.1 ± 2.0 (3)	14.8 ± 7.0 (22)	12.1 ± 8.1 (4)	15.0 ± 7.4 (16)	10.1 ± 3.1 (13)	0	10.1 ± 3.1 (13)
4.	19.1 ± 5.8 (16)	19.7 ± 8 (13)	10.3 ± 1.1 (3)	16.4 ± 9.6 (22)	12.8 ± 8.7 (4)	17.5 ± 10.2 (18)	8.7 ± 2.1 (11)	0	8.7 ± 2.1 (11)
5.	18.4 ± 7.1 (16)	18.6 ± 7.8 (13)	17.7 ± 6.8 (3)	19.7 ± 10.5 (22)	22.3 ± 12.7 (7)	18.8 ± 8.8 (18)	12.3 ± 7.4 (9)	0	12.3 ± 7.4 (9)
Total	17.0 ± 6.2	17.4 ± 7.2	10.2 ± 2.2	15.3 ± 7.9	14.0 ± 6.7	15.1 ± 7.3	10.2 ± 3.6		10.1 ± 3.8

Table 26. Mea MSD (msec) for the i fants in groups I II nd III for th intubated and sponta eously breathi g infants in these groups.

Day	RDS I Total msec ± SD (No of infants)	RDS I Not intubated msec ± SD (No of infants)	RDS I Intubated msec ± SD (No. of infants)	RDS II Total msec ± SD (No. of infants)	RDS II Not intubated msec ± SD (No. of infants)	RDS II Intubated msec ± SD (No. of infants)	RDS III Total msec ± SD (No. of infants)	RDS III Not intubated msec ± SD (No. of infants)	RDS III msec ± SD infants) (No. of infants
1	11.8 ± 3.1 (17)	10.9 ± 2.2 (15)	12.1 ± 3.0 (3)	10.4 ± 3.4 (22)	10.4 ± 2.7 (12)	9.4 ± 2.1 (10)	8.9 ± 2.6 (16)	7.8 ± 4.0 (3)	9.1 ± 2.7 (13)
2	9.8 ± 1.8 (17)	9.6 ± 1.8 (14)	11.0 ± 2.0 (3)	9.6 ± 2.2 (22)	8.6 ± 2.0 (6)	10.0 ± 2.5 (16)	9.4 ± 2.5 (16)	0	9.4 ± 2.5 (16)
3	10.9 ± 2.1 (17)	10.7 ± 2.2 (14)	11.7 ± 2.0 (3)	10.0 ± 2.1 (22)	8.8 ± 2.0 (4)	10.4 ± 2.1 (18)	8.7 ± [illegible] (13)	0	8.7 ± 2.2 (13)
4	12.1 ± 4.3 (16)	12.0 ± 4.5 (13)	12.3 ± 4.1 (3)	10.4 ± 2.7 (22)	8.7 ± 2.1 (4)	10.7 ± 2.7 (18)	7.5 ± 2.3 (11)	0	7.5 ± 2.3 (11)
5	12.0 ± 2.6 (16)	11.5 ± 2.5 (13)	13.6 ± 2.7 (3)	11.8 ± 3.2 (22)	11.7 ± 4.0 (7)	11.8 ± 2.9 (15)	7.6 ± 2.4 (9)	0	7.6 ± 2.4 (9)
Total	11.3 ± 2.8	10.9 ± 2.8	12.2 ± 2.6	10.4 ± 3.1	9.6 ± 2.9	10.5 ± 3.1	8.4 ± 3.0		8.5 ± 3.0

Table IV Mean RMSSD (msec) for the infants in groups I, II and III for the intubated and spontaneously breathing infants in these groups.

Day	RDS I Total msec ± SD (No. of infants)	RDS I Not intubated msec ± SD (No. of infants)	RDS I Intubated msec ± SD (No. of infants)	RDS II Total msec ± SD (No. of infants)	RDS II Not intubated msec ± SD (No. of infants)	RDS II Intubated msec ± SD (No. of infants)	RDS III Total msec ± SD (No. of infants)	RDS III Not intubated msec ± SD (No. of infants)	RDS III Intubated msec ± SD (No. of infants)
1	14.8 ± 4.8 (17)	14.6 ± 4.9 (15)	13.3 ± 0.4 (2)	12.8 ± 4.2 (22)	12.4 ± 4.7 (13)	13.0 ± 3.6 (10)	11.2 ± 4.6 (16)	9.9 ± 4.9 (13)	11.5 ± 4.6 (13)
2	12.6 ± 2.9 (17)	12.1 ± 2.4 (14)	14.8 ± 2.8 (3)	12.0 ± 4.0 (22)	10.9 ± 2.4 (6)	12.8 ± 4.6 (16)	12.0 ± 4.3 (16)	0	12.0 ± 4.3 (16)
3	13.9 ± 3.7 (17)	13.7 ± 3.7 (14)	13.0 ± 2.0 (3)	13.1 ± 4.0 (22)	11.2 ± 4.5 (4)	12.6 ± 4.6 (18)	11.5 ± 4.1 (13)	0	11.5 ± 4.1 (13)
4	15.8 ± 6.3 (16)	15.6 ± 6.7 (13)	16.4 ± 5.1 (3)	13.3 ± 3.3 (22)	11.0 ± 3.8 (4)	13.8 ± 3.2 (18)	9.7 ± 2.9 (11)	0	9.7 ± 2.9 (11)
5	15.1 ± 3.1 (16)	14.6 ± 3.0 (13)	17.2 ± 3.1 ([illegible])	15.6 ± 1.2 (22)	15.0 ± 6.3 (7)	15.6 ± 3.9 (15)	9.9 ± 2.9 (9)	0	[illegible] ± 2.9 (9)
Total	14.4 ± 3.9	14.1 ± 3.8	15.7 ± 2.8	13.3 ± 3.4	15.0 ± 3.9	13.6 ± 3.6	10.9 ± 3.7		10.9 ± 3.8

Heart rate variation in the special RDS groups

a) Expired infants

A total of 8 infants succumbed during the observation period and three a little afterwards. The mean heart rate was all the time a little higher in the expired in fants compared to the surviving RDS in fants ($p < 0.001$).

In the RMSM there were significant differences during the first two days between the expired (11.2 ± 4.1 msec) and the surviving infants (13.1 ± 5.8 msec) but the standard deviation was large. The MSD values were close all the time, al though there were mathematically signifi cant differences ($p < 0.001$) between these groups. The RMSSD was significantly ($p < 0.001$) higher for the expired infants (14.3 ± 5.4 msec) than for the surviving RDS infants (12.8 ± 4.0 msec)

In the discriminant analysis using the birth weight, RMSM and the RMSSD as discriminators there were 16 infants among the surviving ones who were replaced and put in the group of succumbed infants (16/44 = 36 % of the surviving infants) 3 infants from the normal group (11 %) also belonged to this group. Dur ing the second day 3 of the succumbed infants, on the other hand, belonged to the normal group with this analysis.

The index of merit of the classification of all the infants into surviving and ex pired infants was 44 %.

b) Icteric RDS infants

15 patients among the 55 RDS infants belonged to this group The differences between groups Icts and NonIcts were very small in the mean heart rate and in the heart rate variations.

c) RDS infants of mothers with diabetes mellitus

The 5 infants in group D had a sig nificantly lower mean heart rate (129 ± 15 beats/min) than the 50 infants in group NonDs (141 ± 14 beats/min) A differ ence was also seen in the RMSM between group D (20.7 ± 10.6 msec) and group NonD (14.0 ± 6.3 msec) ($p < 0.001$). In group D the MSD was significantly greater only during the second, third and

Table 28. Possibility to predict the death of the infants on the basis of the heart rate variation. Index of merit analysis.

Expired infants

Clinical group (No. of infants)	Correct positive		Correct negative		Index of merit of the method
	No. of infants		No. of infants	%	%
RDS (55) infants	8/11	73	30/44	68	41
RDS (55) infants Normal (28) infants	8/11	73	55/72	76	49
RDS (55) infants Normal (28) infants Isoxsupr (10) infants	8/11	73	58/82	71	44

fifth day ($p < 0.001$) and correspondingly the RMSSD was greater ($p < 0.001$) on the same days than for group NonD 3 of the 5 infants in group D belonged to the normal group with the discriminant analysis during the first day (Fig 16).

d) RDS infants whose mothers had toxemia during the pregnancy

There were only small differences between group T (6 infants) and group NonT (49 infants) in the mean heart rate. Also in the RMSM and the RMSSD the differences were slight.

e) Infants delivered by caesarean section

The mean heart rate was (134 ± 15 beats/min) significantly lower in the group of infants delivered by caesarean section, group CS» compared to the infants who were delivered vaginally group NonCS» (141 ± 15 beats/min) ($p < 0.001$).

During the first five days of life the RMSM in group CS was 20.8 ± 9.4 msec, and in group NonCS 18.4 ± 5.9 msec. The difference was significant ($p < 0.001$) as also in the MSD since the MSD was 11.8 ± 2.4 msec in group NonCS The RMSSD was correspondingly 16.1 ± 3.0 msec and 12.8 ± 4.3 msec and the difference was significant ($p < 0.001$). In the discriminant analysis 5 (56 %) infants in group CS» belonged to the normal group during the first day (Fig. 16).

Four patients who presented a clinical syndrome of decerebration

All the cortical and obviously the subcortical activity as well was absent according to the EEG and the clinical findings in these 4 children presented here as a reference None of these children breathed spontaneously and consequently all of them were on respiratory therapy The frequency of the respirator was 40 cycles/min for the first infant (age 1 week) and 20 cycles/min for the others. For these decerebrated children the RMSM (8.0 msec), the CV (1.4) and the CVS (1.8 %) were significantly shorter than in the RDS group (14.4 ± 7.4 msec, 3.4 ± 1.2 % and 3.0 ± 1.0 % correspondingly). There were no differences in the RMSSD between the groups.

A periodic variation in the heart rate was seen very regularly in all the decerebrated children. The duration of the period was 3.5 sec for the youngest child and for the others 6.5, 6.1 and 6.0 sec respectively

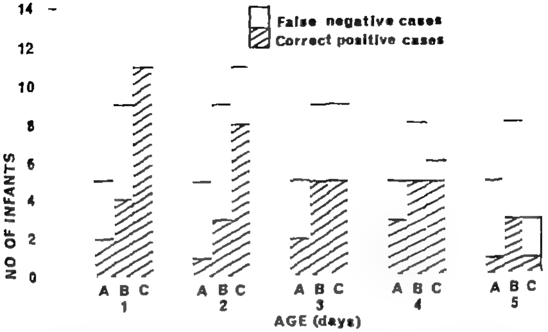

Fig. 16. Column A = group D (diabetes). Column B = group CS (caesarean section). Column C = group EX (expired infants) Classification of the infants in groups D CS, and EX into correct positive RDS infants (P) and into false negative infants (N) using the discriminant analysis with the RMSM and the RMSSD as discriminators. The ruled area in the columns includes the number of correct positive infants

T ble 29 Heart rate (beats/mi), mean R R interval (msec), CV (%), RMSSD (msec), CVS (%), skewness, kurtosis ad the duration of one period i the rate comparison between the mean val e of these for the decerebrated children and fo the RDS group.

Variables	Decerebrated children No 1 7days old	No 2 1month old	No 3 8years old	N 4 13years old	Total group mean	RDS mean ± SD
Heart rate (beats/min)	163	138	64	144	122	140 ± 18
Mean R R interv (msec)	391	435	1102	416	586	433 ± 47
RMSM (msec)	[illegible]	8.7	10 5	8.4	7 4	14 4 ± 7 4
CV)	2 0	1 3	0 9	1.3	1 4	3 4 ± 1.2
RMSSD (msec)	10 6	7 7	11.9	6.5	9.2	10.2 ± 3 2
CVS	2 7	1 8	1 1	1.6	1.8	3.0 ± 1 0
Skewness	0 13	0 04	0 12	0.47	0 2	0.2 ± 0 1
Kurtosis	0 93	10 1	— 0.04	1.22	0.6	0 8 ± 0.1
Periodicity (sec)	3 5	6 5	6 1	6 0	5 5	5.1 ± 1 7
Frequency of respirator (cycles/min)	40	20	20	20		66

DISCUSSION AND CONCLUSIONS

Until fairly recently such findings as cardiac murmurs, ECG and roentgenographic abnormalities have been the most important determinants in the clinical cardiology of neonates. However during the last decade an additional possibility to study the activity of the heart has been developed. Observations of the heart rate variations give information about the heart and the disturbances in the regulation of the cardiovascular system. Thus the heart rate variation also gives information of the cortical and subcortical activity of the infants.

The fundamental knowledge of the heart rate variation was supplied by the visual analysis of long-term recordings (84, 124). Since then numerous investigations of the perinatal heart rate variations have been done by the group in the Biophysics Laboratory of Dalhousie University and by others (26, 81, 125 122, 134 126 127).

During the last twenty years the RDS has been the most interesting syndrome to investigate in clinical neonatology. Recently however most of the interest has been focused on the pulmonary surfactant of the fetus and the neonates (141). Only some investigators have stressed the importance of the cardiovascular system in the development of RDS (24, 52, 58, 97). Are the abnormalities in the cardiovascular system of the RDS infant a reason or a consequence? In any case they are one of the most important features in the development of RDS.

In the present study the correlation between the clinical findings and the heart rate variation was investigated in 55 RDS infants using long term ECG recordings and computer analysis. The system seemed to be feasible and well suited for use in a neonatal ward. It can be used when studying long-term ECG recordings and especially heart rate variations. However it should be observed that extrasystoles and other abnormalities in the ECG makes analysing the heart rate variations inaccurate with the present computer program.

Regulation of the cardiovascular system and heart rate variation in premature and RDS infants

The regulation of the cardiovascular system depends on a servomechanism between the regulatory centres and the heart (20 52, 86, 72, 144). According to Downing (36) the neural regulation of the cardiac performance is important. When the high cortical and subcortical influences on the autonomic centres are blocked, the cardioregulatory centres remain at an abnormally high level of activity (1). If there is a lesion in the medulla, the cardioregulatory centres can be completely suppressed (functional demedullation) and the heart rate is no longer regulated by external stimuli. In sheep fetuses the activity of β-receptors develops later than that

of α-receptors (140). It is not known whether a similar maturation occurs in man as well. However isoxsuprine (β-sympathomimetic) has been found to increase the fetal heart rate (116). During the fetal period there is in the adrenal medulla much more noradrenaline (NA) than adrenaline (A) as compared to neonates or adults (28 29 76). Furthermore according to Naeye et al (92) the adrenal in infants who died of RDS is 1/ / lighter than in the infants dying from other reasons.

Hypoxia and hypercapnia, seen in the RDS reduce the response of the cardiovascular system to cathecolamines (CA) and may enhance the parasympathetic influence (36 49 65). Vagotomy may produce hyaline membranes in certain animals (13, 14). There is also evidence of medullary damage, involving the dorsal vagal nucleus, associated with prematurity and RDS (13) Thus there are many speculations about the dominant role of the autonomic nervous system in the pathogenesis of RDS (23, 52, 93, 121)

In any case it is certain that because of e pathological features (hypoxia, acidosis), RDS infants mobilize all the possible means of defence. On the basis of this the fixed heart rate may be explained by the following hypotheses

1) The receptor activity may be poor or attenuated (140)
2) It is possible that the regulatory centres of the cardiovascular system are suppressed (107)
3) There is a continuous overshooting sympathetic stimulation (22 23)
4) The heart is not capable to respond to stimuli (21 71 76)

On the basis of th u k the observations repo d t r s t study

Mean heart rate In the present investigation the mean heart rate (133 ± 14 beats/min) and the mean R R interval (437 ± 47 msec) in the normal group are in agreement with previous findings (132). In the RDS group the mean heart rate was significantly higher than in the normal group (140 ± 15 beats/min). Respectively the mean R R interval (433 ± 47 msec) was significantly shorter than in the normal group These differences were not seen in the study of Välimäki (132) Furthermore the mean heart rate was during the observation period significantly higher in clinical group III than in group I. That of group II was between these two border groups, so the mean heart rate seemed to be the higher the more severe the RDS was.

The RDS infants were intubated immediately if the infants showed signs of acidosis or hypoxia and perhaps this also accelerated the heart rate. During the first day the group of intubated infants had a higher mean heart rate than the spontaneously breathing infants. On the other hand, the intubated infants were in a worse condition and had therefore more sympathetic stimulation than the infants in a better condition.

Minimum and maximum R R interval. In the minimum R R interval there were no significant differences between the groups. This means that it in every group was possible to increase the heart rate similarly However the maximum R R interval was shorter in the RDS group than for the normal infants, corresponding to the fact that the number of bradycardiac episodes in the RDS group was smaller or less grave than for the normal infants.

Heart rate as a discriminator between the normal and the RDS group

Between the groups there were significant differences in the mean heart rate.

It varied very much, however on the basis of birth weight and gestational age and in the discriminant analysis the heart rate had the lowest discrimination coefficient (page 42).

Fixed heart rate in decerebrated infants

According to Chapman (21) the heart rate became fixed at a rate of 125 beats/min in total cardiac denervation in dogs. In the present study similar fixed heart rate patterns were seen in the decerebrated children. With the present system it was impossible to find any fluctuations in the heart rate because in these children the RMSM was 8 msec and the system error on an average 7 4 msec (page 23) According to the EEG and clinical findings all activity in the cortical parts of the brain was absent and also all fluctuations in the heart rate measured with the present system were finished.

Fixed heart rate in RDS infants

A similar fixed heart rate, like that in these decerebrated children, has been seen in a deep coma and in RDS (137) Desmond et al (35) have described a depressed reflex activity in RDS and a decreased activity in the EEG of asphyctic infants has also been observed (43). When considering the severity of the RDS decrease in the RMSM was also found in this study Rudolph et al suspected (107) that this occurred under the influence of a depression the cortical centres. In severe hypoxia and acidosis in RDS it is probably true, but on the other hand, the heart itself appears also to have the ability to decrease the inherent rate of the sinus node. It is possible to agree with the hypothesis of Cheek et al (22) according to which there is a sympathetic overstimulation. However with β-sympatheticomimetics it is possible to accelerate the heart rate even in the most severe RDS (64)

During the course of the RDS the infant s heart rate may become remarkably fixed. It means that the heart rate does not change during spontaneous activity or when external stimulation is applied (foot thumping) Välimäki (122) defined the pathological fixation of the heart rate quantitatively as an overall variation (RMSM) < 15 msec or a coefficient of variation (CV %) < 5 % in a 500-interval sample. According to my findings these values are quite suitable with some restrictions. The basic error level of the RMSM was in the present system on an average 7 4 msec probably because of the nonstationary tape speed. It can vary in different tape recording systems. So the value of the pathological RMSM must be estimated with every system separately In the smallest premature infants a fixed heart rate seems to be common without any signs of distress and perhaps we cannot in these cases talk about a pathological fixed heart rate. It seems to be a normal feature in many premature infants indicating immaturity Furthermore the smallest infants have a higher heart rate than the term infants. the variation is the smaller the higher the heart rate is. This effect can be eliminated with the value of the CV but in this study the CV did not seem to give any discriminating help in addition to the RMSM and the RMSSD One possibility to avoid this conflict would be to use also a »coefficient of birth weight or gestational ge» when considering the fixed heart rat It means, that if the term or l rge infant has a fixed heart rate this i a more dangerous sign than in the care of the smallest premature infant. Theref the birt weight has been used in

that cyanosis is a poor nonspecific indicator of the difficulties of RDS infants. The value of this parameter has also been criticized in other studies (31).

Heart rate variation and RDS subgroups. RDS includes a relatively heterogenous group of infants and so it was tried in this study to find some special features in RDS subgroups. The mean heart rate and variation in the RDS subgroups differed from those in the total RDS group only in groups D and CS (page 59) The infants in group D were delivered by caesarean section, all except one, so we must find the possible deviations, probably originating from the caesarean section. In these groups the mean heart rate was clearly lower and the RMSM and RMSSD greater than in the total RDS group. The birth weight and gestational age were greater in these groups than in the total RDS group but in spite of these restrictions there must be some special reasons for this difference. These groups differed widely from the total RDS group. The correlation between the clinical classification and the classification on the basis of the heart rate variation was not good. The possible reason for this may be

1) The infants delivered by caesarean section selectively (done before the contractions of the uterus and the rupture of the amniotic membranes) have more total water than the infants born vaginally (19) This can be one of the reasons leading to the development of RDS (130).

2) These infants have no time to adapt themselves to extrauterine life. During the adaptation time the infants born vaginally

a) increase their cortisol level (9), b) enhance the lung maturation and lose excess water from the body (9)

On the basis of these hypotheses the adaptation time for these infants does not begin until after the delivery resulting in an exhaustion of the autonomic nervous system, because the supply of oxygen from the mother is no longer available. Consequently the infants from groups CS and D have lost the adaptation time (151) and have either depleted cathecolamines of the adrenergic nervous system (29), or the response of the receptor system or the heart to stimuli is not adequate. We can talk about a delayed transitional adaptation time of the autonomic nervous system. These infants delivered by selective caesarean section do not show asphyxia before the delivery and they have intact cardiovascular centres, which results in a normal central nervous control and large heart rate fluctuations seen in the infants in the present study

Heart rate variation in the expired infants before death

No typical heart rate patterns were seen in the expired infants before their death. During the first day of life all of them had a fixed heart rate, but afterwards some had fluctuations in the heart rate more than what is typical for an RDS infant (Fig 16, Page 64) Bradycardias and other irregularities in cardiac action in severely asphyctic infants have been mentioned by many investigators (2, 132) Also in the present study the infants were before dying in a bad condition and there were arrhythmias more than in the infants in a better condition reflecting obviously the bad condition of the heart muscle itself. So with this monitoring system we cannot predict accurately enough which infants will die. The index of merit for this system was 44 % for all the infants. Nowadays also many of the worst RDS infants survive if there are not some additional factors like cere-

bral haemorrhagia or pneumothorax. The infants dying because of RDS are not always in the worst condition without these additional factors. No typical heart rate pattern was seen in the expired infants. The heart rate fixation is not in the worst state until the infants are decerebrated, if they are still alive. The same feature was seen also in the infants who developed pneumothorax, there were no typical features in the heart rate patterns.

Usefulness of the present method as a diagnostic help in RDS

In medicine there are only a few single methods with which to make a diagnose. When making a diagnose the physician must use both clinical and many laboratory and physical findings. Neither is a fixed heart rate alone a good indicator of the state of an infant. With the smallest premature infants, who seem to be in a good condition, the fixed heart rate obviously does not mean any great danger. However with sick infants, who seem to have only slight clinical disturbances, but who have a fixed heart rate, the latter can be an indicator of danger of neurological damages. When using such clinical findings as cyanosis, retractions and the breathing, it is not easy for a physician to estimate the severity of the RDS. It would be important to be able to predict which ones of the RDS infants will need respirator or drug therapy (115). Several scoring systems have been used. One of the most useful ones is to estimate the P O_2 when the infants have breathed 100 per cent oxygen (118, 120). It is possible to measure the cord total protein (12) the lactic acid (10) the acid base balance and do a chest X ray (112, 148). It has been tried also with EEG to obtain information about the brain function in asphyctic infants (43 56) None of these systems has proved to be good enough alone. In the present study the clinical state and heart rate variation of the RDS infants have been correlated. Roughly there could be seen a positive correlation between the decrease in heart rate variation and the severity of the RDS. Shifting from one clinical group to another was quite frequent (Table 19 Page 43) Altogether 20 (38 /) of the infants were misclassified, but in border groups I and III there were only 4 (12 /) infants who shifted to other groups. In any case the fixed heart rate reflects the condition of the regulatory centres of the cardiovascular system and the condition of the heart itself. Therefore the decrease in heart rate variation is useful when estimating the state of the RDS infants. In addition the other clinical findings must, of course, also be observed.

SUMMARY

The investigation was concerned with working out the heart rate variation of RDS infants with the aid of long term ECG-recordings and mini-computer analysis. The method used proved reliable and suitable for studies carried out in a neonate ward. In practical work, however the on-line system should rather be used. The weakness of the method employed is primarily in the moderately great error caused by the equipment.

The material for the investigation comprised [illegible] RDS infants and [illegible] healthy infants plus 10 premature infants, whose mothers received isoxsuprine during the delivery The following were the most important findings

1) The heart rate was greatest for the most seriously afflicted RDS infants, but the heart rate of the small premature infants was also greater than that of the term healthy infants.

2) In the group of healthy infants the heart rate variation decreased the smaller the premature infants involved. Most distinctly however the heart rate variation decreased in the RDS infants and the decrease was lightest in the decerebrated infants, for which the error caused by the equipment matched the heart rate variation of these infants

3) Of the quantities used in the investigation the RMSM (th [illegible] variation) decreased most [illegible] during the first day During the [illegible] however the RMSSD (the beat to-beat variation) had the best discrimination coefficient. According to this it can be concluded that along with the overall variation, also the responsiveness of the heart to stimuli started to decrease during the second day of life in the RDS infants.

4) The heart rate variation decreased in the RDS infants as their condition deteriorated. Thus the clinical RDS classification and the classification on the basis of the heart rate variation tallied reasonably well, though there was also some divergence.

5) The infants, whose mothers received isoxsuprine during the delivery had a noticeably slight heart rate variation. The infants in this group were smaller premature infants than in the other groups, but still part of the decrease in heart rate variation could be explained by the effect of the drug

6) The infants of diabetic mothers and those delivered by caesarean section differed most distinctly from the other RDS infants. In these infants could irrespective of the RDS be seen a considerable heart rate variation. The explanation could be that for the infants delivered by caesarean section the adaptation of the autonomic nervous system and the cardiovascular system starts abruptly after the section whereas the infants delivered vaginally may have a considerable time for adaptation when the oxygen supply is still ensured with the aid of the placenta.

7) When using the heart rate variation in separating the RDS and the normal infants from each other during the first five days of life, 49 of the 55 RDS infants showed an RDS-type decrease in the heart rate variation, on the other hand also 6 infants among the 28 healthy infants showed an RDS-type decrease in the heart rate variation. During the first day of life 12 RDS infants had a normal heart rate variation.

8) In the infants who later died, there was directly during the first day a substantial decrease in the heart rate variation. However a corresponding decrease could be seen in several other RDS infants, and the reliability of the method as regards predicting death was not for this reason very good. The same was true concerning the pneumothorax infants.

9) The method used is suitable for following the condition of RDS infants together with the other means of examination and it demonstrates disturbances in the regulation of the autonomic nervous system better than many of the methods now in use.

ACKNOWLEDGEMENTS

The present study was carried out in the Department of Paediatrics and in the Cardiorespiratory Research Unit, University of Turku, Turku, Finland.

The subject was part of the perinatal research project which Professor Tuomas Peltonen, M.D Head of the Department of Paediatrics Director of the Cardiorespiratory Research Unit has carried out in the University of Turku. He aroused my interest in neonatal medicine and his extensive knowledge of clinical and experimental cardio-pulmonary neonatology has been of great help to me during the course of my investigation for which I am deeply grateful to him.

The subject of this study was suggested to me by Dr Ilkka Välimäki, M.D M.Sc., Associate Professor of Paediatrics who has throughout given me invaluable support and encouragement. His knowledge of ECG monitoring has been availabe to me from the beginning, as well as constructive criticism during the preparation of the manuscript. I wish to express my heartfelt gratitude to him.

I am greatly indebted to Professor Pentti Rautaharju, M D Ph.D Professor of Physiology and Biophysics, Dalhousie University Canada, and Professor Jan van Bemmel, Ph.D Professor of Medical Informatics, Free University Amsterdam, Holland, for their criticism of my work.

My thanks are also due to Professor Kaarlo Hartiala, M.D Head of the Department of Physiology and to Professor Lauri Rauramo, M.D H ad of the Department of Obstetrics and Gynecology who made it possible for me to work in their departments.

My warmest thanks are due to Dr Kari Antila, M.D whose experience in biomedical computer application has been an indispensable aid and many methodological problems were solved due to his kind advice and co-operation.

I am greatly indebted to Dr Siinto Jäykkä, M.D Docent of Neonatology University of Turku, who has given me much valuable advice and shown stimulating interest in my work.

I wish to thank Mr Seppo Ahokas, B.A., for the statistical treatment of the results, Miss Heilin Aaltonen and Mrs. Raili Majuri for their secreterial assistance.

My sincere thanks are due to Miss Britt Louise Karlsson for revising the English text.

I thank Mrs. Aili Ryynänen, M.A., and the staff of the Library of the Medical Faculty for their help in collecting the literature.

I want to express my thanks also to the staff of the Department of Paediatrics, the Department of Obstetrics and Gynecology and the Cardiorespiratory Research Unit for the routine work throughout this study

I gratefully acknowledge the financial support from Medica medical factory Helsinki, Finland, and from the Finnish Medical Society Duodecim.

August 1974

Pentti Kero

REFERENCES

1. ADOLPH, E. F., Capacities for regulation of heart rate in fetal, infant, and adult rats. *Am J Physiol* 209 1095, 1965.
2. AHVENAINEN E. K. & LANDTMAN B Asphyxia neonatorum. *Ann Med I tern Fenn* 43 Suppl 18, 34, 1954.
3. AMBRUS, C. M., WEINTRAUB, D.H. & AMBRUS, J L. Studies on hyaline membrane disease. 3. Therapeutic trial of Urokinase-activated human plasmin. *P diatrics* 32 231 1963.
4. ANTILA, K., HALKOLA, L. & VÄLI MÄKI, I. Performance of special-purpose computerized heart-rate monitoring system Evaluation of measurement accuracy *I* National Meeting on Biophysics and Biotechnology in Finland, 1 Helsinki 1973. Proceedings, p. 162.
5. AULD P HODSON, A. & USHER, R. Hyaline membrane disease A discussion. *J Pediat* 80 129 1972.
6. AVERY M. E. The lung and its disorders in the newborn infant. Saunders, Philadelphia 1968, 2nd ed pp. 143—163.
7. AVERY M. E. What is new in our understanding of perinatal pulmonary problems? *Pediatr Res*, 7 842, 1973.
8. AVERY M E. & MEAD J Surface properties in elation to telectasis and hyaline membrane disease. *Am J Dis Child*, 97 517 1959
9. BAUER, C. R., STERN L. & COLLE, E. Prolonged rupture of membranes associated with decreased incidence of respiratory distress syndrome Pediatrics, 53 7 1974
10. BECA, J P & SCOPES, J W Serial determinations of blood lactate in respiratory distress syndrome. *Arch Dis Child*, 47 550, 1972
11. BEMMEL, J H van Detection and processing of foetal electrocardiograms. Nijmegen, Thesis, 1968
12. BLAND R. D. Cord-blood total protein level as a screening aid for the idiopathic respiratory-distress syndrome. *N Engl J Med*, 287 9 1972.
13. BUCKINGHAM, S., SOMMERS, S. C. & SHERWIN R. P., Lesions of the dorsal vagal nucleus in the respiratory distress syndrome. *Am J Clin Pathol*, 48 269, 1967
14. BUCKINGHAM, S., SOMMERS, S. C. & McNARY W F Experimental respiratory syndrome. I. *Biol Neonate* 12 261 1968.
15. BURNARD E. D. Changes in heart size in the dyspnoeic newborn baby *B Med J* 1 1495, 1959.
16. BRUMLEY G W The critically ill child The respiratory distress syndrome of the newborn. *Pediatrics* 47 758, 1971.
17. CALDEYRO-BARCHIA, R., IBARRA POLO A. A., GULIN L., POSEIRO J J & MENDEZ-BAUER, C. *Diagnostic and prognostic significance of intrapartum fetal tachycardia and type II Dips. I* Mack, H. C (ed) Prenatal life. Wayne St Univ Press, Detroit 1969 p. 129.
18. CAPITANIO M. A. & KIRKPATRICK, J A., J Roentgen examination in the evaluation of the newborn infant with respiratory distress. *J Pediatr* 75 896, 1969
19. CASSADY G. Effect of cesarean section on neonatal body water spaces. *N Engl J Med*, 285 887 1971.
20. CASSELS, D. E. (ed.) Heart and circulation in the newborn and infant Grune Stratton, New York 1966, p. 426
21. CHAPMAN C. B. On the nature of cardiac control. *Ann Intern Med*, 53 1272. 1960.
22. CHEEK, D. B., MALINEK, M. & FRAILLON J M.: Plasma adrenaline and nor adrenaline in the neonatal period. *P*

infants with respiratory distress syndrome and placental insufficiency *Pediatrics, 31* 374 1963.

23. CHEEK, D B. & ROWE, R. D Aspects of sympathetic activity in the newborn, including the respiratory distress syndrome. *Pediatr Clin N Am, 13* 863, 1966.

24. CHU J CLEMENTS, J A., COTTON E. K., KLAUS M. H., SWEET A. Y & TOOLEY W H. Neonatal pulmonary ischemia. I. Clinical and physiological studies. *Pediatrics, 40* 709 1967

25. CHU J CLEMENTS, J A., COTTON, E., KLAUS, M. H., SWEET A. Y THOMAS, M. A. & TOOLEY W H. The pulmonary hypoperfusion syndrome. Preliminary report. *Pediatrics 35* 733, 1965.

26. CHURCH, S. C., MORGAN B C., OLIVER, T K., Jr & GUNTHEROTH, W G Cardiac arrhythmias in premature infants An indication of autonomic immaturity? *J Pediat 71* 542, 1967

27 CLYNES, M. Use of computers for physiological discovery and for diagnosis by dynamic simulation. Circ. *Res 11* 515, 1962.

28. COMLINE, R. S., SILVER, I. A. & SILVER, M. Factors responsible for the stimulation of the adrenal medulla during asphyxia in the foetal lamb. *J Physiol (Lond), 178* 211, 1965

29 COMLINE, R. S. & SILVER, M. Development of activity in the adrenal medulla of the foetus and new-born animal. *Br Med Bull, 22* 16, 1966.

30. CORDERO L., J Heart rate changes during the first hour of life. *Biol Neonate 20* 270 1972.

31. CRAWFORD J S., DAVIES, P & PEARSON J F Significance of the individual components of the Apgar score. *Br J Anaesth 45* 148, 1973.

32. DANILOWICZ, D RUDOLPH, A. M. & HOFFMAN J I. E. Delayed closure of the ductus arteriosus in premature infants. *Pediatrics 37* 74, 1966.

33. DAWES, G S Foetal and neonatal physiology Year Bk Med, Chicago 1968, p 247

34. deSA, D J The effects of maturation nd prenatal hypoxia on the pulmonary and body fluid content and lveolar lining layer of foetal rabbits and their relevance to the respiratory distress syndrome *B J Exp Pathol, 50* 42, 1969

35 DESMOND M. M., KAY J L. & MEGARITY A. L. The phases of transitional distress occurring in neonates in association with prolonged postnatal umbilical cord pulsations. *J Pediatr 55* 131 1959

36. DOWNING S. E. Neural regulation of circulation during hypoxia and acidosis with special reference to the newborn. *Fed Proc, 31* 1209 1972.

37 EKELUND H., HEDNER, U & NILSSON I M. Fibrinolysis in newborns. *Acta Paediatr Scand, 59* 33, 1970.

38. FEDRICK, J & BUTLER, N R. Certain causes of neonatal death. I. Hyaline membranes. *Biol Neonate 15* 229 1970.

39 FISHMAN A. P Respiratory gases in the regulation of the pulmonary circulation. *Physiol Rev 41* 214, 1961.

40 GANDY G JACOBSON W & GAIRDNER, D. Hyaline membrane disease. I. Cellular changes. *Arch Dis Child 45* 289 1970.

41 GLUCK, L. Surfactant 1972. *Pediatr Clin N Am, 19* 325, 1972.

42 GLUCK, L., KULOVICH, M. V BORER, R. C., Jr BRENNER, B. H., ANDERSON W G & SPELLACY W N Diagnosis of the respiratory distress syndrome by amniocentesis. *Am J Obstet Gynecol 109* 440, 1971.

43 GRAZIANI L. J WEITZMAN E. D. & PINEDA, G Visual evoked responses during neonatal respiratory disorders in low birth weight infants. *Pediatr Res 6.* 203 1972.

44. GREGORY G A., KITTERMAN J A., PHIBBS, R. H., TOOLEY W H. & HAMILTON W K. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. *N Engl J Med, 284* 1333 1971

45 GRIBBE, P HIRVONEN L., & PELTONEN T Cineangiocardiographic studies of puppies and full-grown dogs. *Acta Physiol Scand, 51* 169 1961.

46. GRIBETZ, I FRANK, N R. & AVERY M. E. Static volume-pressure relations of excised lungs of infants with hyaline membrane disease, newborn and stillborn infants. *J Clin I vest, 38* 2168 1959

47 HANSSEN A. W & KUIPERS, W J A On the relationship between the frequency of rain and various meteorological parameters (with reference to the problem f objective forecasting) Meddelingen en

verhandelingen no. 81 1965 Royal Netherlands Meteorological Institute, Bilt, Netherlands.

48. HARDIE, G HARRISON V C. and KENCH, J E. Further observations on serum proteins in respiratory distress syndrome of the newborn. *Arch Dis Child, 43* 471, 1968

49 HIGGINS, C. B VATNER, S. F & BRAUNWALD E. Parasympathetic control of the heart. *Pharmacol Rev 25* 119 1973

50. HINKLE, L. E. J CARVER, S. T & STEVENS, M The frequency f asymptomatic disturbances of cardiac rhythm and conduction in middle-aged men. *Am J Cardiol, 24* 629 1969

51. HINKLE, L. E. Jr MEYER, J STEVENS, M. & CARVER, S. T Tape recordings of the ECG of active men. Limitations and advantages of the Holter Avionics instruments. *Circulation 36* 752, 1967

52. HIRVONEN L., KOIVIKKO A., LÄNSIMIES, E. & PELTONEN T Neurovegetative Probleme beim Neugeborenen. *Kinderaerztl Prax 41* 291 1973.

53. HOLTER, N J New method for heart studies. *Science 134* 1214 1961

54. HON E. H. & LEE, S T Electronic evaluation of the fetal heart rate. VIII. Patterns preceding fetal death, further observations. *Am J Obstet Gynecol 87* 814, 1963.

55. HON E. H. & QUILLIGAN, E. J Electronic evaluation of fetal heart rate IX. Further observations on pathologic fetal bradycardia. *Clin Obstet Gynecol, 11* 145, 1968.

56. HRBEK, A., KARLSSON K., KJELLMER, I., OLSSON, T & RIHA, M Cerebral reactions during intrauterine asphyxia in the sheep. II. Evoked electroencephalogram responses *Pediatr Res, 8* 58, 1974

57 INALL, J A BLUHM, M. M KERR, M. M., DOUGLAS, T A HOPE, C S & HUTCHISON J H. Blood volume and haematocrit studies in respiratory distress syndrome f the newborn. *Arch Dis Child, 40* 480 1965

58 JÄYKKÄ S Capillary erection and lung expansion *Acta Paediatr Scand, 45* Suppl 112, 1957

59 JÄYKKÄ, S The haemodynamic factor associated with lung expansion t birth *Ann Paediat Fenn, 10* 113, 1964

60. JONES R. S. & OWEN-THOMAS, J B. Care of the critically ill child. Arnold, London 1971 pp. 183—221

61 KALSNER, S., Mechanism of hydrocortisone potentiation of responses to epinephrine and norepinephrine in rabbit aorta. *Circ Res 24* 383, 1969

62. KEITH, J D ROSE, V BRAUDO, M. & ROWE, R. D. The electrocardiogram in the respiratory distress syndrome and related cardiovascular dynamics. *J Pediatr 59* 167 1961.

63. KERO P HIRVONEN T VÄLIMÄKI I. Prenatal and postnatal isoxsuprine and respiratory-distress syndrome. *Lancet, 2* 198, 1973.

64. KERO P & PELTONEN, T., Unpublished data. International Congress of Paediatrics, 14 Buenos Aires 1974.

65 KOIVIKKO A. Cardiovascular response of the neonatal lamb to hypoxia, hypercapnia and metabolic acidosis. *Acta Paediat Scand*, Suppl *191* 1969

66 KRAHL, V E. Evidence of pulmonary arteriolar constriction and arteriovenous shunting in pulmonary hypoperfusion syndrome. (Respiratory distress syndrome f a newborn) *Adv Microcircul 2* 1, 1969

67 KRAHL, V E. Pulmonary vasculature Mechanism controlling the peripheral circulation of the lung with some clinical correlations. *In* Simon, M., Potchen, E. J & Le May M. (eds.) Frontiers of pulmonary radiology Grune & Stratton, New York 1969 p. 169

68 LAUWERYNS, J M. Hyaline membrane disease in newborn infants. Macroscopic, radiologic, light and electron microscopic studies. *Hum Pathol, 1* 175, 1970.

69 LAUWERYNS, J M. Hyaline membrane disease A pathological study of 55 infants. *Arch Dis Child, 40* 618, 1965

70 LAUWERYNS, J M CLAESSENS, S & BOUSSAUW L. The pulmonary lymphatics in neonatal hyaline membrane disease. *Pediatrics, 41* 917 1968

71 LEVY M. N IANO T & ZIESKE, H Effects of repetitive bursts of vagal activity on heart rate. *Circ Res, 30* 1[illegible] 1972.

72 LIGGINS, G C. & HOWIE, R N A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics, 50* 515 1972

73 LIPP J A. M. & RUDOLPH, A. M. Sympathetic nerve development in the rat and guinea-pig heart. *Biol Neonate 21* 76, 1972.

74. LIPTON E. L., STEINSCHNEIDER, A. & RICHMOND J B. Autonomic function in the neonate. VII. Cardio-pulmonary observations. *Pediatrics 33* 212, 1964.

75. LIPTON E. L., STEINSCHNEIDER, A. & RICHMOND, J [illegible] The autonomic nervous system in early life. *N E gl J Med, 273* 147 1965

76. LOGGIE, J M. H. & VAN MAANEN E. F The autonomic nervous system and some aspects of the use of autonomic drugs in children. I. *J Pediatr 81* 205 1972.

77 MAHALANOBIS, P C. On the generalized distance in statistics. *Proc Nat Inst Sci Ind, 12* 49 1936.

78. MARKARIAN M., GITHENS, J H., JACKSON J J BANNON A. E., LINDLEY A., ROSENBLUT E., MARTORELL, R. & LUBCHENCO L. O Fibrinolytic activity in premature infants. *Am J Dis Child, 113* 312, 1967

79 MARKARIAN M JACKSON J J & BANNON A. E. Serial serum total protein values in premature infants with and without the respiratory distress syndrome. *J Pediat 68* 1046 1966.

80 MARTIN J K. A controlled trial of digoxin in the prevention of the respiratory distress syndrome. *Can Med Assoc J 89* 995, 1963.

81. MEIJLER, F L., STRACKEE, J VAN CAPELLE, F J L. & DU PERRON J C. Computer analysis of the RR interval-contractility relationship during random stimulation of the isolated heart. *Circ Res 22* 695, 1968

82. MILLER, [illegible] L. & MARRIOTT H. J L. Office lectrocardiography in general pediatrics. V Arrhythmias (cont.) — pauses and slow heart rates *Clin Pediatr (Phila), 8* 666, 1969

83. MORGAN B. C BLOOM, R S. & GUNTHEROTH, W G Cardiac arrhythmias in premature infants *Pediatrics 35* 658, 1965.

84. MORGAN B C DEANE, P G & GUNTHEROTH, W G Long term continuous lectrocardiographi recording in pediatri patients. *Pediatric 36* 792, 1965

85. MORGAN B. C & GUNTHEROTH W G., Cardiac arrhythmias in normal newborn infants. *J Pediatr 67* 1199 1965.

86. MOSS, A. J DUFFIE, E. R. & EMMA NOUILIDES, [illegible] Blood pressure and vasomotor reflexes in the newborn infant. *Pediatrics 32* 175, 1963.

87 MOSS, A. J & MONSET-COUCHARD M. Placental transfusion Early vs. late clamping of the umbilical cord. *Pediatrics, 40* 109 1967

88. MOTOYAMA, E. K., ORZALESI M. M., KIKKAWA, Y KAIBARA, M WU [illegible] ZIGAS C. J & LOOK, C. D. Effect of cortisol on the maturation of fetal rabbit lungs. *Pediatrics, 48* 547 1971.

89. MOTT J C. Cardiovascular function in new-born mammals. *Br Med Bull, 22* 66, 1966.

90. NADAS, A. S. Pediatric cardiology Saunders, Philadelphia 1963 2nd ed. pp. 64—90.

91 NADRAI, A. Die Elektrokardiographie im Sauglingsalter *Z Kinderheilkd 60* 285 1938.

92. NAEYE, R. L., HARCKE, H. T Jr & BLANC, [illegible] A. Adrenal gland structure and the development of hyaline membrane disease. *Pediatrics 47* 650 1971.

93. NELSON N M On the etiology of hyaline membrane disease. *Pediatr Clin North Am, 17* 943 1970.

94. NIINIKOSKI, J NIKKARI, T & KULONEN E. Pulmonary oxygen toxicity Composition of endobronchial saline extracts of rats during exposure to oxygen. *Aerosp Med, 42* 525, 1971

95 NORDMAND L C. S., REYNOLDS, E. O R., STRANG L. [illegible] & WIGGLESWORTH, J S. Flow and protein concentration of lymph from lungs of lambs developing hyaline membrane disease *Arch Dis Child, 43* 334, 1968

96. PELTONEN T Management of prematures. *Acta Pediat Scand*, Suppl 150 [illegible] 1964

97 PELTONEN T & HIRVONEN L. Experimental studies on fetal and neonatal circulation. *Acta Paediat Scand*, Suppl 161 1965

98. PELTONEN T & HIRVONEN L. Resuscitation of asphyxia in the newborn Physiologic aspects. *Cl: Pediat 4* 644 1965.

99 PELTONEN T & HIRVONEN L. Diskussion über die Entstehung der hyalinen Membranen *Wissensch ftl Z Humboldt U i Berlin, M th N i R, 20* 8? 1971.

100. PELTONEN T & KREINER, E. Untersuchungen über die in vitro zur Entfaltung von Neugeborenenlungen nötigen Druckwerte. *Z K aderhelk*, 86 198, 1961
101. PHILLIPS, S. J AGATE, F J Jr SILVERMAN W A. & STEINER, P Autonomic cardiac reactivity in premature infants. *Biol Neonat* 6 225, 1964.
102. RAUTAHARJU P M. Deterministic type waveform analysis in electrocardiography *Ann NY Acad Sci*, 128 939 1966.
103. REYNOLDS, E. O. R. Hyaline membrane disease. *Am J Obstet Gynecol*, 106 780, 1970.
104. REYNOLDS, E. O. R. Indications for mechanical ventilation in infants with hyaline membrane disease. Pediatrics, 46 193, 1970.
105. REYNOLDS E. O. R ROBERTON N. R. C. & WIGGLESWORTH, J S. Hyaline membrane disease respiratory distress, and surfactant deficiency *Pediatrics*, 42 758, 1968.
106. RUDOLPH, A. J DESMOND M. M. & PINEDA, R. G Clinical diagnosis of respiratory difficulty in the newborn. *Pediatr Clin North Am* 13 669 1966.
107 RUDOLPH, A. J VALLBONA, C & DESMOND M. M Cardiodynamic studies in the newborn. III Heart rate patterns in infants with idiopathic respiratory distress syndrome. *Pediatrics* 36 551, 1965
108. SALAI, T., HÄNNINEN P & PELTONEN T.. The electrocardiograms of premature infants in the first month of lif *Biol Neonate* 2 149 1961.
109 SHANKLIN D R. & LESTER, E. P On the pulmonary toxicity of oxygen II The effect of the second gas *Biol Neonate*, 20 140, 1972
110. SHUMAK, K H. & BROWN K. W G Continuous portable electrocardiography *Can Med Assoc J* 98 179 1968
111. SINCLAIR, J C Prevention and treatment of the respiratory distress syndrome *Pediat Clin North Am*, 13 711 1966
112. SINGLETON E B Respiratory distress syndrome *Progr Ped Radiol*, 1 135 1967
113. SPIEGEL, M R Outline of theory and problems of statistics. Schaum, New York 1962, pp 90—91
114. STAHLMAN M BLANKENSHIP W J SHEPARD, F M GRAY J YOUNG W C & MALAN, A. F Circulatory studies in clinical hyaline membrane disease *Biol Neonat* 20 300, 1972
115. STAHLMAN M. T BATTERSBY E. J SHEPARD F M. & BLANKENSHIP W J Prognosis in hyaline-membrane disease. Use of linear-discriminant. *N Engl J Med*, 276 303 1967
116. STANDER, R. W BARDEN T P THOMPSON J F PUGH, W R. & WERTS, C. E. Fetal cardiac effects of maternal isoxsuprine infusion. *Am J Obstet Gynecol*, 89 792, 1964.
117 STEELE, M. W.. Plasma volume changes in the neonate. *Am J Dis Child*, 103 [illegible] 1962.
118. STERN L. The use and misuse of oxygen in the newborn infant. *Pediatr Clin North Am*, 20 447 1973.
119. STERN L., BEAUDRY P JEGIER, W & SEKELJ P Pathophysiology of the cyanosis in the respiratory distress syndrome. *J Pediatr* 67 1039 1965
120. STERN L. Therapy of the respiratory distress syndrome. *Pediat Clin North Am*, 19 221 1972.
121. STERN, L. & OUTERBRIDGE, E. W Urinary catecholamine excretion in hyaline membrane disease. *In International Congress of Pediatrics*. XIII Vienna 1971. Proceedings, p. 372.
122. SUTHERLAND T M. & YOUNG, D. A. B. Increased permeability of the capillaries of the rat heart to plasma albumin with asphyxiation and perfusion. *J Physiol (Lond)*, 183 112, 1966.
123. SUTIN G J & HEESE, H. de V Electrocardiogram in idiopathic respiratory distress syndrome of newborn *Lancet* 2 832, 1964.
124 SUTIN G J HORNER, R., HEESE, H de V & MALAN A. F The electrocardiogram in respiratory distress syndrome. The praecordial P wave as an aid to assessment. *Arch Dis Child*, 40 402 1965.
125 TARLO P A VÄLIMÄKI, I & RAUTAHARJU P M. Quantitative computer analysis of cardiac and respiratory activity in newborn infants *J Appl Physiol* 31 70 1971.
126 TAEUSCH, W J WYSZOGRODSKI & AVERY M. E. Alterations of pulmonary pressure-volume relationships in the perinatal period Physiologic evidence for release of surfactant at birth *Pediatr Res*, 7 425, 1973.
127 TAYLOR, F M. Respiratory distre

the newborn. *Clin Obstet Gynecol, 14* 763, 1971

128. URBACH, J R., PHUVICHIT B., ZWEIZIG H., MILLICAN E., CARRINGTON E. R., *LOVELAND M., WILLIAMS, J M.*, LAMBERT R. L., DUNCAN A. M., FARRELL, S. L., SIMONS F [illegible] & SPURGEON L. L. Instantaneous heart rate patterns in newborn infants. *Am J Obstet Gynecol, 93* 965 1965

129. USHER, R. The respiratory distress syndrome of prematurity I. Changes in potassium in the serum and the electrocardiogram and effects of therapy *Pediatrics, 24* 562, 1959

130. USHER, R., McLEAN F & MAUGHAN G. B., Respiratory distress syndrome in infants delivered by cesarean section. *Am J Obstet Gynecol*, [illegible] 806 1964.

131. USHER, R SHEPHARD, M. & LIND J The blood volume of the newborn infant nd placental transfusion. *Acta Paediatr Scand*, [illegible] 497 1963.

132. VÄLIMÄKI, I. Heart rate variation in neonates. M Sc. Thesis, Dalhousie University Halifax, *N.S.* 1971.

133. VÄLIMÄKI I. Postnatal alterations of cardiac rhythm. *Clin Pediatr (Phila) 9* 652, 1970

134. VÄLIMÄKI, I. Tape recordings of the electrocardiogram in newborn infants. *Acta Paediatr Scand*, Suppl 199 1969

1 VÄLIMÄKI, I. Heart rate variation in full term newborn infants. I. Use of a small, special-purpose computer *Biol Neonate 18* 129 1971

136. VÄLIMÄKI, I., TARLO P A., SCOTT K. E UNITE, V C. & RAUTAHARJU P M., Computer analysis of long term records of heart rate and respiration rate in newborn infants. *Acta Paediat Scand* Suppl 206 144 1970.

137 VALLBONA, C., CARDUS, D., SPENCER, W A. & HOFF H. E. Patterns of sinus arrhythmia in patients with lesions of the central nervous system. *Am J Cardiol, 16* 379 1965.

138. VALLBONA, C., DESMOND M M., RUDOLPH, A. J PAP L. F HILL, R M., FRANKLIN R. R. & RUSH J B. Cardiodynamic studies in the newborn. II. Regulation of the heart rate *Biol Neonate 5* 159 1963.

139 VALLBONA, C., RUDOLPH A J & DESMOND M. M. Cardiodyn mic tudies in the newborn. IV Heart rate patterns in the nondistressed premature infant. *Pediatrics 36* 560 1965

140. VAPAAVUORI E. K., SHINEBOURNE, E. A., WILLIAMS, R. L., HEYMANN M. A. & RUDOLPH, A. M. Development of cardiovascular responses to autonomic blockade in intact fetal and neonatal lambs. *Biol Neonate* [illegible] 177 1973.

141. *VILLEE*, C. A., *VILLEE*, B. [illegible] & ZUCKERMAN J Respiratory distress syndrome. Academic Press, New York 1973, p. 406.

142. WALSH, S. Z. Early versus late clamping *of the cord A comparative study of the* ECG in the neonatal period. *Biol Neonate* [illegible] 343, 1968.

143. WALSH, S. Z. Electrocardiographic intervals during the first week of life. *Am Heart J 66* 36, 1963.

144 WARNER, H. R. & RUSSEL, R. O., Effect of combined sympathetic and vagal stimulation on heart rate in the dog. *Circ Res 24* 567 1969

145. WELLER, M. H. The roentgenographic course and complications of hyaline membrane disease. *Pediatr Clin North Am, 20* 381 1973.

146 WILLIAMS, C. D & HAUGAARD N Toxic effects of oxygen on cerebral metabolism. *J Neurochem, 17* 709 1970.

147 WOLF H. K. Dynamic behavior of the human sinoatrial node. An analysis of the rate generating process in the absence of external stimuli Ph.D. Thesis, Dalhousie University Halifax, N.S., 1969

148. WOLFSON S. L., FRECH, R HEWITT C. & SHANKLIN D R. Radiographic diagnosis of hyaline membrane disease. *Radiology 93* 339 1969

149 YAO A. C. & LIND J Placental transfusion. *Am J Dis Child, 127* 128, 1974.

150. YAO A. C., WIST A. & LIND J The blood volume of the newborn infant delivered by caesarean section. *Acta Paediatr Scand, 56* 585 1967

151 YOON I. L, & HARPER, R. G Observations on the relationship between duration of rupture of the membranes and the development of idiopathic respiratory distress syndrome *Pediatrics, 52* 161 1973.

152. YOUNG M. Responses of the systemic circulation f the newborn infant. B *Med Bull 22* 70 1966

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STUDIES IN NORMAL MALE PUBERTY

BY *PER ERIK WAALER*, THOR THORSEN
KARL F STØA and *DAGFINN AARSKOG*

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

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231. Stensland Junker, Karin, Selective Attention in Infants and Consecutive Communicative Behavior. 1972
232. Hagne, Ingrid, Development of the EEG in Normal Infants During the First Year of Life. A Longitudinal Study. 1972
233. Wendelin, Hedvig, Microangiography of the Liver. An Experimental Study of Sheep from the Prenatal to the Postnatal Period. 1972
234. Gerrard, J. W., MacKenzie, J. W. A., Goluboff, N., Garson, J. Z. and Maningas, C. S., Cow's Milk Allergy: Prevalence and Manifestations in an Unselected Series of Newborns. 1973
235. Köhler, Lennart, Health Control of Four-Year-Old Children. An Epidemiological Study of Child Health. 1973
236. *Proceedings of the Seventeenth Scandinavian Paediatric Congress*, Reykjavík, 1972. Edited by P. J. Moe. 1973
237. Sillanpää, Matti, Medico-Social Prognosis of Children with Epilepsy. Epidemiological Study and Analysis of 245 Patients. 1973
238. Silver, Jørgen, von Willebrand's Disease in Sweden. 1973
239. Persson, Harriet, The Finnish Skolt Lapp Children. A Child Psychiatric Study. 1973
240. *Rearing of Non-identical Twins with Lymphogenic Hypogammaglobulinemia under Gnotobiotic Conditions.* Edited by W. M. Teller. 1973
241. Sahni, Tahir T. Haptoglobin Levels in the Plasma of Newborn Infants, with Special Reference to Infections. 1973
242. Valkendorf, Tapio, Analysis of Serial Echoencephalograms in Healthy Newborn Infants During the First Week of Life. A Comparative Study by One- and Two-dimensional Echoencephalography. 1973
243. Lundström, Nils-Rune, Clinical applications of echocardiography in infants and children. 1974
244. Ahlström, Hans, Studies on Pulmonary Mechanics in Infants. 1974
245. Iversen, Ulla, Hereditary Nephropathy with Hearing Loss "Alport's Syndrome". 1974
246. Ohrt, Jakob, Training of Medical and Dental Students in Mental Retardation. 1974
247. Hjalmarson, Ola, Mechanics of Breathing in Newborn Infants with Pulmonary Disease. 1974
248. Bergman, Lars, Studies on Early Neonatal Hypocalcemia. 1974
249. Winter, Per Erik, Thorsen, Thor Bjørn, Karl F. and Aarskog, Dagfinn, Studies in Normal Male Puberty. 1974

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ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 251 1974

ON THE PERSONALITY STRUCTURE IN DIABETIC SCHOOLCHILDREN

AGED 7–15 YEARS

BY KERSTIN FÄLLSTRÖM

ALMQVIST & WIKSELL PERIODICAL COMPANY STO[redacted]

ACTA PÆDIATRICA SCANDINAVICA SUPPLEMENT 251

On The Personality Structure in Diabetic Schoolchildren

Aged 7–15 years

BY

KERSTIN FALLSTRÖM

in collaboration with

ORVAR EEG-OLOFSSON

GÖTEBORG 1974

Printed in S eden, Gotab, Kungalv 1974

This investigation has been accomplished in cooperation with doctor Orvar Eeg-Olofsson the Departments of Pediatrics and Clinical Neurophysiology

Doctor Eeg-Olofsson has compiled the clinical data about the patients and has performed the electroencephalographic investigation He has written the passage on the electroencephalographic method The presentation of the EEG findings has been written in close cooperation with doctor Eeg-Olofsson who also during the preparation of the manuscript contributed with valuable comments and discussions.

The EEGs were taken at the department of Clinical Neurophysiology Sahlgrenska Sjukhuset, Goteborg. (Head professor I Petersén)

CONTENTS

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I INTRODUCTION

A chronic disease often has a great impact on the life situation of the individual Many chronic diseases start in early childhood and have a decisive influence on the physical and mental development of the child In this report the personality development of children with diabetes mellitus will be discussed and related to different background variables.

Developmental theories and concepts

In infants and small child en d fferent patterns of behavio can be observed reflecting basic individual differences *In infancy and early childhood* however the personality structure is diffuse and there are no standardized methods to assess it Nevertheless, the experiences of the child during this period are considered to be of fundamental importance for the development of the personality structu e Influenced by F eudian analytic theory Erikson (27 28) states that regardless of subsequent events early emotional impressions have an influence upon the child s behavior and con tinue to have an effect on different aspects of future development

During the first years of life – the sensori-motor phase the repetitive use of reflexes and thei successive integration into more complex reactions and voluntary movements is, according to Piaget (85) the base of future cognitive development. Therefore early brain damage interfering with this eflex activity can have an adverse influence on the developmental process

At the approximate age of three years the child begins to look upon himself as an individual who can influence and be influenced by his environment This means that the personality structure be omes mo e differentiated The child is no longe dominated by impulses and drives – the id according to Freud One portion of the id develops into the ego a part of the personality which acts as a moderator between the id and the external world (41). That is, the child learns to inhibit his impulses according to the expectations of the environment The ego is compa able to the concept self" "me" or "I by other authors (33 57 75). Since it is derived from individual experiences the ego takes cognizance of reality as well as of impulses To a great extent the individual s interaction with his environment in this sense may be conceived as reality testing. In reacting to his environment the child develops not only an ego but also an awareness of right and wrong. This is the basis of the conscience or the superego – the phrase coined by Freud The superego is assumed to be composed of personal experience derived from the ideas and attitudes of sign ficant adults and peers. The task of the ego is to be an agent of reconciliation between the id and the superego The individual s life – his manner of perceiving, feeling and acting – depends largely upon the balance of these three affective aspects – the id the ego the superego In chronic diseases the ego structure may be weakened and the child w ll remain at, or egress to a stage of more uncontrolled behavior and in extreme cases this lack of selfcontrol can lead to desperate actions e g. suicide – total desintegration of self" (105)

An interesting concept in the discussion of personality development is that of body image The body image is one s personal perception and experience of the own body – one s feelings and attitudes towards the physical self It develops out of sensori-motor stimuli and out of the interaction between human beeings At birth there exists no body image and the newborn only has feelings of comfort discomfort hunger pain etc During the first 2 3 years of life the child has no real perception of his body as something sepa ate from the environment As the coordination bet ween sensory and motor functions develops, the child more and more looks upon his body as a separate entity The sensori-motor stimulation

therefore is of great importance for the development of the body image. The child receives cues and signals from his environment that facilitates the development of his body image. This is the base for the child's comprehension of his own person and its relation to his environment (11) and of himself as an individual distinct from other individuals. It is essential for the child to have a stable frame of references for his perception of himself in order to be able to perceive and appreciate other people. In this interaction the ego structure of the child is developing. The stability of this structure is to a great extent depending on the attitudes and reactions of the environment.

In children with cerebral lesions a distorted body image is often found (9). Their perception is impaired because of the faulty feedback they receive from their body in its interaction and integration with the environment. The world is perceived in a twisted fashion, appearing unstable and unpredictable. In cases of brain damage with sensory defects the distorted body image can be regarded as a primary feature of the disease.

Deviations in the development of the body image are common in several chronic diseases, with or without obvious physical defects or functional handicaps (35, 112). Lipowski (73) has discussed the necessity of integrating the disease concept into the personality to achieve a normal development. He claims that if this integration fails, there will be secondary disturbances in the body image. If an individual avoids accepting his illness because of its implications on his life situation, this fact can, according to Lipowski, have serious consequences on his management of the disease and on his adaptation to the situation.

The attitude of the environment, especially of the family, towards the child is of uttermost importance for normal growth and maturity. In a study of thalidomide children (78) it was found that only one child had integrated his cumbersome protheses into his body image. The mother of this child thought that he looked more normal with the protheses than without them. Pankow (81) found a relation between the type of body image disturbance evident in psychotic children and their family structure.

Eriksson (28) divides the psychosocial development into eight stages. He differs from classical Freudian theory and most other developmental theories, in considering personality integration not being reached until adulthood. Most theories assume this integration to take place during adolescence. In the Western society, where the individual seldom reaches independence during adolescence, Eriksson's theory seems to fit better with the factual reality that parental dependence is prolonged. Every stage or crisis, as Eriksson calls them, consists of two conflicting tendencies, one positive and one negative. A normal development means that the positive tendency is dominating in crisis-resolution. However, this does not infer that the negative influence is completely suppressed.

During adolescence the individual passes through an identity crisis, a milestone in the personality development according to Eriksson. This crisis consists of a positive pole – identity – and a negative one – identity diffusion. When a person reaches this stage or crisis he is an individual with a conception of his possibilities and limits as well as of his social position. From this base the adolescent must get his sexual, occupational and adult roles. To succeed the individual needs help from his environment which must provide him with prototypes for positive identification. Sears (91, 92) regards this identification process as a motivational system which induces the young person to behave according to the expectations of the environment. If the environment does not provide opportunities for positive identification the result can be identity diffusion. This means that the individual is uncertain about his future roles in different fields. In some cases this confusion leads to negative identification, that is the individual adopts roles – behavior patterns – which are not accepted by the society, e.g. criminality (28).

Because of the uncertain prospects of his future living, an adolescent with a chronic disease can be expected to have difficulties in finding his identity, leading to identity diffusion (29). One example is identity consciousness, in which the individual constantly is conscious of his own body and appearance and of the impressions he makes on other people. This may interfere with all his social activities and lead to emotional disturbances. If he can not stand this feeling of extreme consciousness – the feeling that everybody is looking at and talking about him – he may withdraw from society.

An individual may be a member of a marginal group because of the special character of his disease (73). An illustration of this situation is the child with a minor motor deficiency attending an ordinary school. Because of his motor disability he cannot take part in all the activities of his classmates, giving him difficulties in finding peers with whom he can identify (88).

Diabetes mellitus and its social implications

Diabetes mellitus is a chronic disease. The interplay of various factors causing the disease are largely unknown. The basic defect is an absolute or relative lack of insulin. This causes dysfunction in the carbohydrate, protein and fat metabolism. Genetic factors predispose to diabetes mellitus. Offspring of diabetic patients stand a higher than average risk of contracting the disease. Cerasi and Luft (18) estimate that 15 % of the Swedish population have a predisposition for diabetes mellitus. Manifest diabetes occurs in one percent of the Swedish population (15). In approximately 4 % of the cases the onset of the disease appears before 15 years of age.

From a clinical point of view two forms of manifest diabetes are usually identified, the juvenile and the adult types. Especially in juvenile diabetes, the metabolic disturbances may lead to an endogenous intoxication due to the accumulation of acid intermediary metabolic products (ketoacidosis). This form of diabetes always requires insulin treatment, although during the initial phase of the disease sometimes diet alone may suffice for a short period. The diabetes in growing individuals and young adults practically always belongs to the juvenile type. Adult diabetes occurs later in life, is less severe and has not the same tendency to ketoacidosis. Insulin treatment is usually not necessary.

The classical symptoms of untreated diabetes mellitus are fatigue, loss of weight, increased amount of urine and thirst. A well controlled diabetic patient should have very few symptoms of his disease. Despite of very good control there is sometimes a reduction of the somatic growth. A serious complication of diabetes is the diabetic coma, which is caused by the endogenous intoxication (ketoacidosis) in combination with dehydration and circulatory failure. Cellular function is disturbed and irreversible cell damage may occur. In this situation insulin treatment is lifesaving. Too large dosis of insulin leads to hypoglycemia (i.e. too low blood glucose level) which causes hunger, palpitations, cold sweat and cerebral disturbances. Severe hypoglycemia leads to unconsciousness, convulsions and sometimes to irreversible brain damage (47).

The life expectance of the diabetic patient is shortened because of vascular complications, the so called angiopathia diabetica (69). These complications appear after about 10–15 years duration of the disease and several organs may be affected. There is an increased risk of cardiac infarction and a high frequency of renal disorders leading to renal insufficiency. The diabetic retinopathy often causes blindness. An insufficient arterial circulation in the legs can lead to gangrene. Both central and peripheral neurological disorders are seen as a consequence of the vascular changes or the basic metabolic defect. Although these complications are uncommon in children and adolescents, they constitute a continuous threat interfering with the future social and occupational plans of the young patient.

In order to obtain good control, the patient with juvenile diabetes must be treated with insulin injections once or twice daily. He must always be on a strict diet, and among other things exclude sweets and cakes, and he must have regular meals. A certain amount of physical exercise is necessary to keep the patient well regulated. Urine analyses for glucose and ketoacids must be done regularly at home and regular visits to the hospital's outpatient clinic are essential. If satisfactory control is not achieved hospital admission may be necessary.

To be able to accept such a regulated life the child needs help from his family. About this Traisman (103) says: "The psychological impact upon the patient and his parents when diabetic mellitus is discovered should be fully recognized by the physician. He must offer reassurance and emotional support to the patient and family during the first hours and days of hospitalization."

In practice, the prognosis of diabetes mellitus is influenced by how the members of the family work together in helping the diabetic child to control his disease. The strict dietary requirements will increase and complicate the mother's work load. It also means sacrifices from the other members of

the family which can arouse hostility and work against a realistic adjustment of the total family. In addition the diabetic diet places an economic burden on the family because it requires the best and therefore most expensive raw materials. The very regular food schedule of the diabetic child can influence his normal peer-interaction and in many ways exclude him from activities that do not fit into his rigid time table. The special diet he will receive in the school refectory will also set him apart from the others.

The need for daily injections is a constant reminder of the problem and can stimulate feelings of disability and inadequacy. Before the child can give himself his injections he is dependent on his parents. During periods of rapid growth such as puberty the necessary amount of insulin as well as the caloric needs change. The patient therefore often requires frequent hospital contacts in order to adjust the insulin dosage and diet. Especially during a vulnerable developmental period such as adolescence this increased need of control is unfortunate and stressful.

Earlier investigations

Although most diabetic children are physically fit and have very few somatic symptoms several authors have stated that the disease has an influence on the emotional adjustment of the children. Benedek in 1948 (10) reported the finding of anxious and depressive behavior in diabetic children which was confirmed by other early investigations (16, 34, 65, 95). These authors suggested different causes for the maladjustment and the reported frequencies of disturbances varied. None of these studies contained a control group. In a broad assessment including projective techniques and interviews Swift et al. (101) compared 50 juvenile diabetics with a matched control group and found significantly more emotional disturbances and poorer social adjustment in the diabetic group. Contrasting with this study is a paper by Sterky (98) in which interviews of diabetic children and matched controls were not able to demonstrate an increased frequency of "mental disturbances" in the diabetic children. However, he found an increased frequency of anxiety symptoms among their mothers. His results are supported by the findings of Wolff & Olatawura (113) who showed that "the emotional burden of the illness in younger diabetic children falls upon their mothers who suffer an excess of nervousness, anxiety and depression". It has been claimed that the attitudes and reactions of the parents have a decisive effect on the child's adaptation to this disease. Bain & Chute (4) and Jochmus (59) found that diabetic children who had anxious and disease conscious mothers were immature, anxious and dependent children.

Investigations on the influence of clinical variables such as age at onset, duration of the disease etc. on the personality are contradictory. It has been stated that an early onset of the disease gives less emotional disturbances because it is easier for the young child to accept his disease (71, 96). Other authors present reports indicating that older children understand and accept the disease and its treatment more easily (83, 94, 116).

Both Sterky (97) and Swift et al. (101) found an association between "poor" control of the diabetic disease and emotional disturbances in the children. Koski (67) also found that children with "good" and "fair" diabetic control had more integrated and imaginative personalities with better differentiated ego bounderies, and more awareness of conventional concepts, than children with "poor" control. However, the relationship between degree of control and emotional status appears to be complex. Vandenbergh et al. (107) showed an increase of blood glucose and free fatty acids following hypnotique induced stress and physical anticipatory stress, and it has been claimed that emotional lability influences the carbohydrate metabolism in diabetes mellitus leading to poor control (7, 43, 102, 104).

Baker & Barcai (6) have suggested the existence of a close association between clinical variables and psychosocial structure and have used a combined clinical and psychosocial evaluation to divide diabetic patients into a number of subgroups. Their definitions, however, appear vague and their system difficult to apply.

In many investigations diabetic children have been found to have an intelligence above average (5, 31, 97, 103, 110) but some investigations have not been able to confirm this finding (68, 74, 94). An attempt to identify a specific diabetic personality has been made (21), but in reviewing the available literature on diabetic children no consis-

tant "diabetic personality structure" has been found.

Electroencephalographic abnormalities (1, 7, 32, 49, 59) and reduction of the nerve conduction velocity (22, 44) have been demonstrated in diabetic children without obvious clinical neurological signs and symptoms. Jochmus (59) made a broad assessment of 78 diabetic children in which clinical, psychosocial and neurophysiological investigations were included. She did not analyse the intercorrelations between the pathological findings.

Thus the literature on the psychosocial aspects of the diabetic disease in childhood is somewhat contradictory. In many investigations only one technique has been adapted and the use of different techniques may explain the contradictory results. It seems that especially the exclusive use of interviews can give an incomplete picture. A few studies with a broad approach including different techniques in the assessment of the child and its environment have been reported but an extensive exploration of the intercorrelations between psychological data and various background factors is lacking. In the psychological appraisal of diabetic children the occurrence of cerebrolesional traits has been paid little attention to and no report on the relation between electroencephalographic abnormalities and the personality structure has been found.

Aim of the study

The aim of the present investigation is to obtain a detailed description of the personality development in a group of diabetic schoolchildren through a broad psychological assessment including an intelligence test, different projective techniques and interviews. In the assessment special regard will be paid to the following:

The development of essential elements in the personality structure such as the body image, the ego structure and the identity processes.

The occurrence of disturbances such as neurotic and cerebrolesional traits.

and

The correlation between clinical variables such as age at onset, duration of the disease and degree of control, and the psychological findings.

An additional purpose of the study is to procure information about environmental attitudes directed towards the diabetic child and the influence of these attitudes on the personality development of the child.

An electroencephalographic (EEG) investigation is included in the assessment of the children particularly stressing the following questions:

What is the frequency of definitely pathological EEG patterns indicating the existence of a cerebral lesion?

To what extent does the diabetic disease have an influence on the development of the normal EEG pattern?

Are there any correlations between EEG abnormalities and deviations of the personality development?

II MATERIAL

In the city of Goteborg[1] patients with diabetes mellitus below 16 years of age practically always are under the care of the staff of the Pediatric Department, Barnklinikerna, Östra sjukhuset (formerly the Children's hospital). In the present study children 7–15 years old with the diagnosis of diabetes mellitus and with duration of the disease exceeding one year were selected from the files of the hospital. When the study was planned 66 children fulfilled these criteria. In 59 cases (27 boys and 32 girls) the child and its parents were willing to participate in the investigation. In 7 cases the families refused to cooperate.

The following reasons were presented for not participating: fear of accentuating the feeling of being ill (3 cases), negative experience of previous hospitalization (cases), aversion to psychological testing (1 case), the timeconsuming element of investigations (1 case). It could be assumed that the family's attitude towards the child was different in these seven cases, but nothing in the records of these seven children indicated any special features of their disease.

The material was classified into children in "excellent", "fair" and "poor" control of the disease (Table 1). This is an internationally used terminology based on fasting blood glucose value, degree of glucosuria, acetonuria and cooperation regarding the diet, physical activity and urine analysis at home (111). In this material the blood glucose level was not estimated regularly at the outpatient clinic visits. The degree of glucosuria was based on the results of a series of urinary tests on 24 hs specimen performed at least 4 times a year. At home glucosuria was assessed with Clinitest reagettes on the second voiding in the morning three times a week. Glucosuria less than 20 g, 20–50 g and more than 50 g per 24 hs characterized the three control groups respectively. The classification mainly considering the degree of glucosuria but with additional regard to the degree of cooperation was done by drs O. Egg-Olofsson & S. P. Fällström and the interscoring reliability of the procedure was estimated at .90.

In Figures 1 and 2 and Table 2 age at onset, age at examination, duration of the disease and degree of control are given for boys and girls separately.

In Table 3 further clinical data relevant to the following discussion are presented. Hypoglycemia with convulsions had been diagnosed three times in two diabetic girls, twice in three boys and three girls, and in the remaining cases only once. Two girls had epileptic fits (psychomotor epilepsia and petit mal respectively) as well. Abnormal delivery included vacuum extraction, forceps delivery and

Table 1 Degree of diabetic control

Group	N	Excellent(I)	Fair(II)	Poor(III)
Boys	27	10(37)	8(30)	9(33)
Girls	32	7( )	13(41)	12(37)

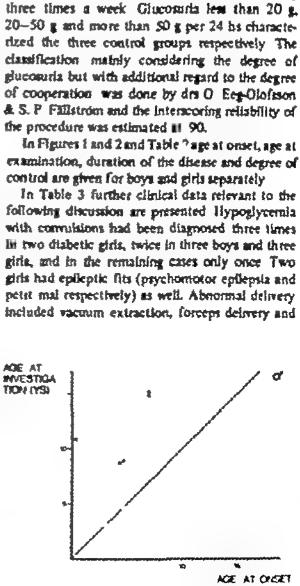

Fig. 1 Age at investigation in relation to age at onset. Vertical distance from the broken line = duration, boys

[1] Number of inhabitants [illegible]

Fig. 2. Age at investigation in relation to age at onset. Vertical distance from the broken line = duration, girls.

Caesarean section. The neonatal complications comprised intra- and extrauterine asphyxia, cyanotic spells and cerebral symptoms. Abnormal delivery and/or neonatal complications occurred in 6 of the boys and in 7 of the girls. The birth weight was below 2 500 g in 7 boys and 3 girls.

The mean number of children in the diabetic families was 2 with the range 1–6 for the girls and 1–7 for the boys. 6 boys and 4 girls were the only child. Mean school marks 3.0 and 3.5 for boys and girls respectively. (School marks are measured by a 5 point scale).

The diabetic children were compared with a matched group of healthy children, the control group. The matching was done considering age, sex and intelligence level. The differences between the matched individuals did not go beyond 3 months of age and 1 stanine score on the intelligence test. The social group distribution in the controls did not differ significantly from that in the diabetic group.

The following abbreviations will be used: Control girls (C_g), control boys (C_b), diabetic girls (D_g), diabetic boys (D_b).

Table 3. Relevant clinical data. Db = diabetic boys, Dg = diabetic girls

	Db (n = 27)	Dg (n = 32)
Diabetes in mother, father and/or sibling	4(14.8 %)	6(18.7 %)
Hypoglycemia with convulsions	12(44.5 %)	10(31.2 %)
Hospitalisations mean	3.3	2.5
range	1–9(26*)	1–7
Birth weight (mean±SD in g)	3588±655	3579±565
Abnormal delivery	5(18.5 %)	4(12.5 %)
Neonatal complications	4(14.8 %)	4(12.5 %)
Concussion (head injury with unconsciousness)	5(18.5 %)	1(3.1 %)
Pertoven before 2 years of age	3(11.1 %)	7(21.9 %)
Social group		
I (8 %)	5(18.5 %)	3(9.4 %)
II (38 %)	12(44.5 %)	17(53.0 %)
III (54 %)	10(37.0 %)	12(37.6 %)

* One boy with serious behavior disturbances had been hospitalized 26 times because of poor diabetic control.

Figures for Goteborg 1968

Table 4. Age at examination, age at onset, duration of disease (in years) and degree of control

Age at examination		N	Age at onset Mean	Range	Duration Mean	Range	Degree of control I	II	III
6.6–9.5	boys	9	3.9	2.1–6.2	4.0	1.1–6.4	4	4	1
	girls	4	4.1	1.5–6.10	4.1	1.1–6.9	3	1	0
9.6–12.5	boys	5	5.3	0.3–9.4	5.2	2.3–10.5	1	3	1
	girls	14	6.5	1.7–10.7	4.5	1.1–10.1	1	8	5
12.6–15.5	boys	13	6.4	1.3–12.7	7.3	1.0–13.3	4	1	7
	girls	14	9.4	3.11–13.4	5.0	1.0–9	3	4	7

III METHODS

The selection of methods for the present investigation aimed at a broad assessment of the personality structure. Techniques were chosen which emphasize basic developmental processes, the presence of cerebrolesional and emotional disturbances.

Psychological tests

The following test battery was used

The Wechsler Intelligence Scale for Children

The Rorschach test

The Blacky Pictures test

The Bender Visual Motor Gestalt test

The psychological assessments were done in the homes of the children. Three advanced students trained by the author tested the children. Scoring of the tests was done by the author without cognizance of the testee.

The administration of the Rorschach test was in keeping with original instructions (89). Scoring and analysis were done according to Bohm (14), and an item-list presented by Holley et al. (50) was used. Interscoring reliability was estimated at .82.

The administration, scoring and analysis of the Blacky Pictures test followed Blum's manual (13). The item-list contains questions of the inquiry and questions about cartoon preferences. Interscoring reliability was estimated at .87.

The Bender test was administered according to Bender (8). Scoring was done by two systems, according to Pascal & Suttell (82) and Hutt (55). The interscoring reliability of this test has been calculated to .90 and .91 respectively (55, 80).

The Rorschach test gives a comprehensive picture of the personality structure (2, 3, 66). In this context the evaluation of the body image development by means of the barrier and penetration scores (35, 36, 37, 38, 39) is of interest. Barrier answers (for instance answers indicating things being covered, surrounded, protected etc.) are a measure of the consistency of the body image bounderies while penetration scores (for example answers indicating body injury) are a measure of disintegration of body image boundaries. The ego structure "quantitative scale" has been obtained through a select usage of combined Rorschach responses (14). The test may also indicate the existence of different neurotic traits such as anxiety and aggression and cerebrolesional traits.

The Blacky Pictures test was originally designed to reveal "underlying psychosexual aspects of personality". Identity is one of these aspects. The test also gives information about the relationship between the family members.

The Bender Visual Motor Gestalt test is usually regarded as a brain damage test. However, brain damage is a heterogenous concept and it is valuable to recall Wortis' statement (114) "There is in short no braindamaged child, but only a variety of brain-injured children whose problems are quite varied and whose conditions calls for more refined analyses than some of the current generalizations on the brain-injured child provide". The Bender test particularly measures perceptual disturbances, which usually are signs of a cerebral lesion, but may occur in children without signs of brain damage.

Comments

Opinions about the value of projective techniques are varying. There are many reasons for this controversy. It is difficult to give a concise definition of personality. The reliability and the validity of personality assessments have often turned out to be questionable. It is difficult to get parallel tests and retesting is sometimes impossible because of effects of memory. Subjective elements are difficult to avoid in the administration and evaluation of the test. A careful analysis of the criterion to be prognosticated (61) and the use of

Table 8. Item content in Blacky Pictures factors differentiating between diabetic children and controls.

No of item related to cartoon	Da III	VI	XIII	[illegible] IV	V	XV	Dg IV	VI	VIII	XIV	XV	Cg VII	IX
1/I													
89/VIII													
94/VIII													
123/IX													
197/II													
198/IV													
199/IV													
12/II													
26/IV													
28/IV													
40/IV													
78/VII													
136/X													
185													
193													
200/III													
201/III													
5/I													
16/II													
29/IV													
35/IV													
42/V													
86/VIII													
128/IX													
144/IX													
145/IX													
4/I													
24/IV													
23/IV													
37/IV													
92/IX													
106/IX													
113/IX													
118/IX													
122/IX													
49/V													
54/V													
57/V													
59/V													
5/VII													
6/VII													
84/VII													
90/VIII													
112/IX													
132/IX													
134/X													
140/X													
146/XI													
167													
187													
191													
202/II													
204													
205													
206													
32/IV													
53/V													
56/V													
95/VIII													
114/IX													
125/IX													
138/X													
177													
Age 6.6–9.5 years	0	0	0	1	2	0	0	0	2	1	0	0	0
9.6–12.5 years	1	0	0	2	1	0	2	0	2	1	2	2	2
12.6–15.5 years	1	4	4	1	3	3	0	2	0	0	0	1	3
Mean duration (in years)	11.3	7.1	[illegible]				5.8	4.8	8.3	6.2	4.9		

scorematrices contained 147 items both for the boys and for the girls. The factors explained 68 % of the total variance for the boys and 73 % for the girls. Rotated factor matrices are given in Appendices IV–V Thirteen factors differentiated between the diabetics and the controls and these factors are presented in Table 8. They were distributed among the groups in the following way Db 3 factors (III VI and XIII) Cb 3 factors (IV V and XV) Dg 5 factors (IV VI VIII XIV and XV) Cg 2 factors (VII and IX) In one factor Dg XIV there are three diabetics and one control.

Factor interpretation

Factor III (Db) indicates strong oral dependence feelings of rejection, aggressions towards the parents and a sense of guilt. The factor denotes unsatisfied need of security

Factor VI (Db) signifies feelings of isolation, wish for contact with the father and feelings of aggression towards the mother This factor is related to age.

Factor XIII (Db) like factor III indicates strong oral dependence and aggression wish for identifying with the father but problems in reaching both him and the mother emotionally This factor is also related to age

Factor IV (Cb) denotes positive identification, sibling rivalry and some oral dependence.

Factors V and XV (Cb). These two factors are similar and indicate good functioning superego father identification and some oral dependence. In factor V is added guilt feeling and a dominant mother figure In factor XV there is a guilt feeling component.

Factor IV (Dg) signifies feelings of parental lack of interest ego-defence anxiety of being hurt, wish to identify with the mother but disappointment in her and identification problems. The factor is related to age.

Factor VI (Dg) denotes sibling rivalry oral fixation, narcissism and a negative ego-ideal. It also stands for feelings of parental lack of interest. The factor is related to age.

Factor VIII (Dg). This factor also indicates feelings of parental passivity and disregard and aggression against siblings. Identification with the father is a possible occurrence.

Factor XIV (Dg) stands for bad relationship with the rest of the family anxiety and guilt feelings.

Factor XV (Dg) means identification with the father but a passive one without devotion and anxiety about the future. This factor is related to age

Factors VII and IX (Cg) demonstrate positive relations between the members of the family and a good super-ego but some jealousy of the parents.

Comments

Like the Rorschach test, the Blacky Pictures reveale significant differences between the diabetic children and the controls, signifying that a disturbed psychosexual development is more frequent in the diabetic group The themata of the spontaneous stories are about isolation, feelings of neglect, sibling rivalry oral dependence and negative expectations for the future There are obvious indications of identity problems. The content of the differentiating factors unanimously gives the same picture.

The differentiating factors comprise 36 % of the diabetic children. The "strong" spontaneous stories reveal emotional disturbances of the above mentioned types in additional 25 % of the diabetic group The analysis of individual test records, however, discloses less pronounced disturbances in most of the remaining diabetic children. It is especially notable that these children, who to a high degree depend on their family for the management of their disease so often give responses indicating poor family relationships. In the controls obvious disturbances of the psychosexual development are found in 3 boys and 4 girls. Signs of less pronounced deviations are found in 5 children in the control group

The Bender Visual Motor Gestalt test

In Table 9 are given mean values for Bender items scored according to Pascal-Suttell, differentiating between diabetic children and controls. In all these items the diabetic group gives more abnormal respones. Eighteen boys and 15 girls in the diabetic group and 2 boys and 1 girl among the controls represent these responses. Considering all items 21 boys and 24 girls in the diabetic group and 5 boys and 6 girls of the controls present one or more deviating responses.

Table 10 shows the mean values for Bender items scored according to Hutt. Also this type of scoring discloses definite differences between the diabetics and the controls. With this type of scoring deviating responses can be demonstrated

Table 9. Mean values for differentiating Bender items (Pascal Suttell) in diabetic children and controls. Not significant differences denoted by parenthesis.

Item		D	C	Db	Cb	Dg	Cg
Design I	Work over	(0,27	0,17)	0,30	0,06	(0,25	0,13)
Design II	Work over	0,20	0,01	0,11	0,03	0,30	0,00
Design III	Asymmetry	0,27	0,06	0,33	0,03	(0,25	0 10)
	Distortion	0,76	0,05	0,74	0,03	0,80	0,07
	Work over	0,43	0,00	0,40	0,00	0,56	0,01
Design IV	Asymmetry	0,46	0,01	0,45	0,01	0 47	0,01
	Distortion	0,45	0,00	0,40	0,01	0 50	0,00
Design V	Asymmetry	0,34	0,07	0,48	0,01	(0,_0	0,15)
	Rotation	0,38	0,00	0,39	0,00	0,38	0,00
	Distortion	0,24	0,00	0,01	0,01	0,50	0,00
	Work over	0,34	0,09	0,34	0,00	(0,35	0,18)
Design VI	Asymmetry	0,43	0,05	0 41	0,09	0,48	0,01
	Distortion	0,57	0,09	0,45	0,18	0,69	0,00
	Work over	0,81	0,00	0,78	0,00	0,84	0,00
Design VII	Rotation	0,49	0,00	0,54	0,00	0,45	0,01
	Distortion	0,30	0,02	0,30	0,01	0,31	0,0_
Design VIII	Rotation	0,88	0,02	0,94	0,00	0,82	0 03
	Distortion	0,89	0,12	0,87	0,14	0,9	0,11
	Work over	0,53	0,08	0,63	0,12	0,34	0,04
No order		1,36	0,09	1 48	0,10	1,25	0,08

C [illegible] 59
Cb Db 27
Cg Dg 32

Table 10. Mean values for Bender items (Hutt) in diabetic children and controls. Significant differences ($p < 0.05$) denoted by asterisks.

Item	D	C	Db	Cb	Dg	Cg
Orderly sequence	2,42	6,56	2,22	6,44	2,59	6,62
Normal position (1 D)	1,15	2,18	1,33	2,16	1,00	2,19
Use of space	2,80*	4,07	3,33	3,61	2,40*	4 46
Collision	3 05	3,46	3,07	3,27	3 03	3,62
Shift of paper	2,39	2,63	2,50	2,38	2,31	2,85
Closure difficulty	5,38*	2,41	5,74	2,97	5,08	1 93
Crossing difficulty	2,20	2,09	2,44	2,72	2,03	1,56
Curvature difficulty	4,35	2,64	4,88	3,25	3 90	2,12
Change in size and angulation	5 69*	2,50	5,51	2,92	5,84	2 15
Perceptual rotation	3,08	2,05	3,33	2,22	2,87	1,90
Regression	2,02	2,16	2,66	2,55	1 46	1,84
Simplification	1,87	2,01	2,11	2,66	1,65	1 46
Fragmentation	1 11	1,81	1,22	2,44	1,00	1,28
Overlapping difficulty	1,61	1,36	2,00	1,80	1,28	1,00
Elaboration	1 11	1,55	1,22	1,88	1,00	1 17
Perseveration	2,68	1,59	2,88	1 97	2,50	1.28
Redrawing	1 99	2,10	1 92	1,89	2,06	2,27

C D 59
Cb Db 27
Cg Dg [illegible]

not only in all the diabetic children but also in several of the controls. Some pathological items (simplification and fragmentation) are even more frequent in the controls. Therefore scoring according to Hutt seems to make the test a more sensitive instrument.

Comments

According to Pascal-Suttell (82) the Bender test measures two kinds of deviations, psychogenic disturbances and deviations depending on organic changes. Especially "distortion" "rotation" and "asymmetry" are items related to brain damage. According to Hutt high scoring on "change in size and angulation" "perceptual rotation" and "perseveration" indicate organic disturbances. Both types of items are more frequent in the diabetic group than in the controls.

The diabetic group displayed no permanent clinical neurological symptoms or signs. The frequent findings of cerebrolesional traits in the Bender test are therefore of particular interest, especially with regard to the reported electroenphalographic abnormalities in diabetic children (22 32, 49 59)

However with either scoring method the test also measures other dimensions. The Hutt adaptation of the Bender test is an attempt to use the procedure as a projective device. This means that the test besides indicating cerebrolesional traits also gives information about emotional disturbances. "Orderly sequence" "change in curvature" "closure difficulty" and "rotation" are items which have been claimed to reveal emotional maladjustment. All these items are significantly more frequent in the diabetic group.

Interviews

All 58 mothers (two diabetic girls were siblings) could participate in the interview. Five mothers were single and another 10 fathers were unable to take part in the investigation. Thus 43 fathers were interviewed. The information about the children's behavior and problems which emerged from the interviews of the parents and teachers is summarized in Tables 11–13. In Table 14 are given the children's opinions and attitudes towards their situation.

Table 11 Behavior deviations according to the interview with the parents.

Symptom	Scoring		Db Father No	%	Mother No	%	Dg Father N	%	Mother No	%	Cb Mother No	%	Cg Mother N	%
School problems[1]	No	(1)	17	85,0	9	33 3	14	61,0	13	40,6	24	88,9	29	90,6
	Yes	(2)	3	15,0	18	66 7	9	39 0	19	59 4	3	11 1	3	9 4
Peer problems[1]	No	(1)	15	75,0	17	63,0	16	69,5	18	46,2	24	88,9	28	87,6
	Yes	(2)	5	25 0	10	37,0	7	30,5	14	43,8	3	11 1	4	12,4
Aggression[1]	Seldom	(1)	12	60,0	16	59 3	15	65,2	20	62,5	21	81,8	30	93,8
	Often	(2)	8	40,0	11	40,7	8	34 8	12	37,5	6	22,2	2	6,2
Introvert	No	(1)	12	60,0	15	55,6	13	56,6	15	46,9				
aggressive behavior	Yes	(2)	8	40,0	12	44 4	10	43,4	17	53 1				
Reaction to	Not anxious	(1)	15	75,0	20	74 1	18	78,3	21	63 7	26	96 4	28	87,6
stranger[1]	Anxious	(2)	5	25,0	7	25,9	5	21 7	11	36,3	1	3,6	4	12,4
Reaction to	Not anxious	(1)	14	70,0	21	77,8	17	74,0	26	81,2				
policlinic visit	Anxious	(2)	6	30,0	6	22,2	6	26,0	6	18,8				
Reaction to	Not anxious	(1)	4	20,0	12	44 4	7	30,5	13	40,6				
hospitalization	Anxious	(2)	16	80,0	15	55,6	16	69,5	19	59 4				

1) Questions given to the mothers of the controls

Table 12. Behavior deviations in the diabetic children according to the interview with the teacher

Symptom	Scoring	Db Teacher No	%	Dg Teacher No	%
School problems	No (1)	12	44,4	13	40,6
	Yes (2)	15	55,6	19	9 4
Peer problems	No (1)	18	66,7	12	37,5
	Yes (2)	9	33,3	20	62,5
Problems in the school refectory	No (1)	[illegible]	66,7	27	84 4
	Yes (2)	9	33,3	5	15 6

Table 13. Behavior deviations in the diabetic children according to the doctor's interview

Symptom	Scoring		Db No	%	Dg No	%
Paroxysmal headache	No	(1)	24	88,9	22	68,7
	Yes	(2)	3	11 1	10	31,3
Paroxysmal abdominal pain	No	(1)	24	88,9	26	81 2
	Yes	(2)	3	11 1	6	18,8
Nailbiting, tics, pavor nocturnus, stuttering	No	(1)	15	55 6	13	40,6
	Yes	(2)	12	44 4	19	59 4
Aggression	No	(1)	17	63,0	19	59 4
	Yes	(2)	10	37,0	13	40,6

Comments

It is obvious that the parents differ in their opinions about school and peer problems of the diabetic children. The fathers seem much less aware of such problems. The teachers and the mothers however show good agreement about the existence of problems. In the area of peer difficulties the children themselves reveal the highest frequency of problems. The parents opinions about signs of aggression and anxiety correlate better especially in the first mentioned symptom.

Although only three of the diabetic children showed behavior disturbances severe enough to warrant contact with a child psychiatrist, the interviews demonstrate a high frequency of adaptation problems in terms of conventional child psychiatric symptoms. As a matter of fact very few (2 boys and 3 girls) of the diabetic children had no symptoms of that kind. The frequency of behavior deviations seems very high and probably several cases with only slight adjustment problems

Table 14. Information obtained in the interviews of the children.

		Db No	%	Dg No	%	Cb No	%	Cg No	%
Reaction to first information about the disease	Worry for the future	4	14 8	9	28 1				
	No events	7	25,9	7	21 9				
	Fear of injections	2	7 4	2	6,2				
	Too young to understand	14	51,9	14	43,8				
Greatest problem	Worry for the future[1)]	13	48,1	14	43,8				
	Diet	1	3,8	9	28,1				
	Injections	2	7 4	1	3,1				
	Peer or school problems	3	11 1	3	9 4				
	Have no great problems	8	29,6	5	15,6				
Spontaneously expressed wish to be healthy[1)]		6	22,2	9	28,1				
Activities after school[2)]	Mainly outdoors	19	70,4	18	56,3	17	63,0	15	46 9
	Mainly indoors	8	29 6	14	43 7	10	37,0	17	53 1
Takes physical exercise regularly		22	81,5	23	71,9				
Have informed classmates about the disease		26	96,2	27	84 4				
Have peer problems[1, 2)]		13	48,1	21	65,6	4	14,8	3	9 4
Definite occupational plans[2)]		[illegible]	81,5	28	87,5	17	63,0	22	68 7

1) In the correlation analyses, peer problems, wish to be healthy and worry for the future are scored 2, their absence scored 1

2) Questions given to the control children.

are included. The results should, however be compared with those of Koski (67) Swift et. al. (101) and Jochmus (59), all reporting a high frequency of maladjustment in diabetic children. Furthermore the results are in agreement with the high frequency of deviating responses in the personality tests.

In the control group significantly lower frequencies of school and peer problems and aggressive and anxious behavior are found (Table 11). These figures are in agreement with those reported by Johnsson & Kälvesten (60), who have investigated a group of unselected schoolboys aged 7–15 years in Stockholm.

Thus the diabetic disease apperently influences the adaptation of the children. Despite good intellectual capacity school problems are frequent and the social contact with classmates and friends are made difficult, the latter probably by the necessary strict diabetic routine. Secondary neurotic symptoms manifested as aggression and anxiety are also common. The indication is seen in the answers on direct questioning or indirectly by symptoms such as tics, nailbiting etc. The presence of recurrent headache and/or abdominal pain may also signify the same type of maladjustment.

About half the number of the diabetic children were too young at the onset of the disease to understand its nature and consequences. However several of the children already at that time were worried about their future and subsequently an increasing number feel the uncertainty of the future as their greatest problem. However compared with the control group the diabetic children more frequently have definite ideas about their future occupational activities. Plans for medical and/or nursing occupations dominate among the diabetic girls (46.9 %) and occur significantly more often than in the control girls (20 %). About one third of the boys express unrealistic plans of future careers as professional athletes. Fear of injection does not seem to be a frequent problem at any time. Relatively many girls experience the diabetic diet as their main problem.

In many areas the diabetic children share the hobbies and interests of healthy children. Their interest in outdoor activities does not seem to be less pronounced. About a quarter of the diabetic children admit that they despite the doctor's advice do not take physical exercise regularly though. A spontaneously expressed wish to be healthy was mainly found in the older children. Diabetic children do not hesitate to inform their classmates about their disease.

Correlations between the psychological assessment of the diabetic child and clinical data

In order to limit the number of variables for the correlation analyses indices were constructed from the personality data, Table 15. The neurotic index contains 6 Rorschach items which are common in neurotic patients. The cerebrolesional index comprises 5 Rorschach items which have been found to be associated with brain damage (14). The perceptual disturbance index includes 4 Bender items with high correlation to brain damage (82). The maladjustment index contains 5 Bender items which have been found to differentiate between children in need of psychotherapy and well adjusted children aged 7–15 years (17). The identity index is the number of stories scored "strong" on cartoons VII, X and XI in the Blacky Pictures test.

From the interview data an anxiety index was constructed comprising the manifestation of anxious reaction to strangers, to policlinical visits and to hospitalizations and the presence of indirect evidence of anxiety such as tics, nailbiting etc.

In addition to these indices, following Rorschach phenomena and scores are included in the correlation analyses: "paranoid traits" "object criticism" "emotional lability" "aggressivity" "oral preoccupation" and "ego weakness" (dichotomized), "penetration" and "barrier". Isolated responses indicating ego weakness are found in practically all diabetic children. A weak ego structure should, however implicate a serious deviation of the personality development, and therefore, only those children giving more than five such responses are scored on "weak ego structure".

The above mentioned psychological data have been selected, because they differentiate between the diabetic children and the controls and because they give information about fundamental developmental processes and common emotional disturbances. Their occurrence in the individual cases is given in Appendices VI and VII.

Table 15 Personality indices and their content.

		KR_{20}
Neurotic index (Rorschach)	Color-red- and Cd-shocks, resignation, black and white as colors, defect-answers	.959
Cerebrolesional index (Rorschach)	Perseveration, inhibition, delimination, commentary uncertainty	.870
Perceptual disturbance index (Bender)	Distortion, rotation, asymmetry, work over	.756
Maladjustment index (Bender)	Sequence: orderly, change in curvature, closure difficulty, rotation, over-all change in size and angulation	.977
Identity index (Blacky Pictures)	Spontaneous stories scored "strong" on cartoons VII, X, XI	.786
Anxiety index (Interview data)	Reactions to strangers, to polyclinic visit and to hospitalizations; the presence of symptoms such as excessive nailbiting, tics, pavor nocturnus, stuttering	.830

In Table 16 are given correlations between clinical information about the diabetic disease and the results of the psychological assessment. Table 17 presents the relationship between peri- and postnatal events and the psychological data. The correlations between the psychological assessment and symptoms revealed by the interviews are shown in Table 18.

Comments

Good mental capacity is correlated to good control of the disease and few hospitalizations – a natural association. The correlation between intelligence and low age at onset in the boys is of interest from genetic point of view with regard to the more than average mental capacity found in the diabetic group. The lack of correlation in the girls may be an effect of the skew distribution of the material with relatively few early onsets in the girls (Fig. 2).

Long duration of the disease and many hospitalizations are associated with signs of disturbed body image development (significant correlations to barrier and penetration scores) and the identification processes.

Emotional lability is related to early onset, long duration and hypoglycemic convulsions. Otherwise most of the significant correlations are found in the girls between hypoglycemic convulsions and signs of cerebral lesion and emotional disturbances.

The sex difference is interesting, since hypoglycemic convulsions are as frequent among the boys as they are among the girls. The higher frequency of personality deviations in the girls may depend on the skew age distribution in the groups and/or a real sex difference in the personality structure. Both these factors may imply a more "mature" reaction in the girls.

In the diabetic children few significant correlations are found between peri- and postnatal events, and personality deviations (Table 17). The relation between perceptual disturbances and previous head injury in the boys is of interest. The personality disturbances to a higher degree seem to be related to the course of the diabetic disease than to these other clinical events.

Close correlation is found between the results of the personality tests and the psychiatric symptoms disclosed in the interviews (Table 18). Information about anxious reaction in different situations is correlated to neurotic traits and signs of disturbed body image in the Rorschach test, signs of maladjustment in the Bender test and identification problems in the Blacky Pictures. Both school and peer problems are related to body image disturbances. School problems are also correlated with cerebrolesional and neurotic traits, while peer problems are correlated to emotional lability and signs of aggressivity in the Rorschach test.

Table 16 Correlations between clinical and psychological data.

	Age at onset			Duration			Degree of control			No. of hospitalizations			Hypoglycemia with convulsions		
	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
WISC	23	.34	.09	06	31	16	40	− 29	−.53	19	− 22	−.37	− 05	− 01	− 09
Neurotic I	11	−.23	03	.22	41	12	12	03	.21	.05	21	.04	23	17	.38*
Cerebrolesional I	01	.07	− 22	01	07	04	03	− 13	− 05	− 07	− 17	.08	13	−.28	43
Perceptual disturbance I	.08	− 11	11	− 01	04	.01	02	04	08	−.01	− 08	− 02	.38	11	.58
Maladjustment I	14	.26	− 11	02	−.5	06	05	10	03	−.02	18	.08	40	18	.56
Paranoid Trait	− 12	.34	05	05	12	05	01	04	05	−.06	− 01	− 06	31	− 04	.53
Object criticism	12	17	− 19	07	02	10	01	06	−.02	−.05	−.08	.03	29	13	.55
Emotional lability	− 31	− 48	.28	47	.34	.52	08	02	07	11	.24	.20	.33	.28	.54
Aggressivity	.04	15	.21	.21	32	09	− 02	13	19	.27	47	− 01	−.01	.03	.01
Oral Preoccupation	−.08	.07	− 12	.05	.07	06	.02	13	.03	−.05	− 17	.03	.33	.28	.54
Penetration	.01	.00	.05	16	.20	.05	.02	.21	− 19	.05	44	− 19	13	.27	.05
Barrier	10	03	13	29	16	40	23	10	.20	11	20	14	05	− 25	30
Ego weakness	17	−.31	04	20	38	05	11	16	05	05	− 13	33	08	.02	25
Identity I	.07	.01	17	.32	24	40	30	31	.31	.27	40	10	− 19	−.20	−.20

* $p < 0.05$

T total material (n = 59)
Db boys (n = 27)
Dg girls (n = 32)

	n=59	n=27	n=32
Confidence level .01	34	.53	48
.05	.26	40	.36

appropriate statistical methods e.g. G-index (52, 53) have been found to increase the reliability and validity of personality tests. Eron (30) is of the opinion that if content is defined as an essential element of the Rorschach protocol the mystery of the expert's interpretation may surrender to scientific scrutiny. Levitt et al (72) and Fisher & Cleveland (35) have demonstrated the advantages of content scoring in the Rorschach test. Sappenfield (90) points at the relative lack of structure of the Blacky Pictures, the single hero figure available for identification and possible drawbacks with the name "Blacky". But he is of the opinion that dimensional scoring is of great value and also stresses that it is useful to determine specifically how the testee responds to each situation (cartoon). In spite of the difficulties associated with projective techniques these are widely used in research and with the above mentioned modifications the techniques can be expected to give valid and significant information.

Interviews

Semistructural questionaries were used. The questions are given in Appendix I. For feasible presentation and statistical analysis the answers were scored in the categories given in the appendix.

Parents

The parents were interviewed in their home at the time of the assessment of the child. In cases of chronic diseases the mother is thought to have specific influence on the child's reactions to his disease (113). Therefore the parents were interviewed separately in order to demonstrate possible differences in their attitudes. The interview was constructed to assess the following areas.

The attitudes of the parents towards the diabetes and its treatment, including injections, diet and daily routine

Principles of child rearing, with special regard to rigidity overprotection and level of interest

The opinion of the parents about the child's behavior with regard to signs of aggression, anxiety school problems etc.

Applicable parts of the questionary were used for an interview with the mothers of the control children.

Teachers

The teachers had a telephone interview. The questions aimed at evaluating the following matters

The teacher's cognizance about the child's disease

The teacher's opinion about the child's behavior and capacity

The contact with the parents.

Children

The children were interviewed at the time of the psychological testing. The interview assessed the following areas

Activities outside the school.

Reactions towards the disease

Expectance of the future.

Applicable questions were given to the control group.

In connection with the EEG investigation parents and children were interviewed by the physician about vegetative symptoms (attacks of headache and/or abdominal pains) and symptoms such as tics, excessive nailbiting, stuttering and pavor nocturnus.

Electroencephalographic (EEG) investigation

The diabetic children participated in a longitudinal EEG study which will be reported separately (26). Thus, most of the children had passed through two or more EEG investigations, and only eight of the children were administered EEG for the first time.

The EEG patterns undergo a characteristic development during the growth of the individual. This development has recently been studied in detail in a transversal study comprising 743 children – 389 girls and 354 boys aged 1–15 years – selected on the basis of 13 criteria of normality (23 24 25 84). The results of a subgroup of this investigation comprising 491 children – 66 girls and 255 boys aged 7–15 yeas – will be used for a comparison with the EEG records of the diabetic group. These children will be referred to as "controls" (C').

EEG-technique

The EEGs were taken with a Kaiser electroencephalograph. In most cases 8 channels were used for the EEG and 2 for recording eye movements. The *10–20 electrode system of the International Federation* was used with the customary longitudinal and transverse bipolar derivations. In all recordings one montage with a common reference lead (homolateral ear) was also used. The paper speed was 3 cm/sec the time constant 0.3 sec and the filter 70 Hz. The procedure was as follows

Recording at rest usually occupied the initial 30 minutes, if the subject did not fall asleep at the outset of the registration Running notes have been made for the resting EEG regarding the occurrence of drowsiness of the subject. Alerting stimuli such as visual stimuli i.e. eye opening or eye winking, auditory stimuli or fist clenching, were performed several times during the recording

Hyperventilation was performed for 3 minutes. The subjects were encouraged to draw as deep breaths as possible and a respiration rate of about 20/min was obtained. The recording was continued until 2 min after hyperventilation

Intermittent photic stimulation was carried out by means of a Kaiser stroboscope (electrical energy = 0.2 joule/flash maximum intensity at 10 flashes/sec 1 8 megalux). The lamp distance was 15 cm. Flashes were produced in the following sequences *"rising course"* – 4 6 8 11 15 20, 24 flashes/sec each frequency lasting 40 sec *"declining course"* – 20 18, 16 15 14 12, 11 10 8 6 4 flashes/sec, each lasting 20 sec, 4 flashes/sec and 24 flashes/sec alternatively for 3 sec on 10 consecutive occasions, and finally 15 flashes/sec 6 times for 5 sec, with an interval of 15 sec between each stimulation period.

Sleep records including a run of about 10 to 20 minutes light sleep were kept. When sleep was not achieved spontaneously it was induced by oral administration of barbiturate (mebumal sodium) 7–11 years. 80–110 mg, 12 years and more 100–150 mg. The dosage also depended on the weight of the subject and the degree of alertness.

Blood glucose concentration was determined by capillary method (glucose oxidase) before and directly after the EEG recording which in most cases was performed between 1 and 4 p.m. Information had been given in advance in order to avoid the influence on the EEG of hypoglycemia, raised body temperature and fatigue To avoid hypoglycemia the children were told to eat a full meal one hour before the procedure Mean blood glucose concentration ±1 S.D before and after the investigation was 271±128 and 248±128 mg per 100 ml respectively In none of the children hypoglycemia occurred The EEG records were analyzed according to the method described by Petersén and EEG-Olofsson (84).

Statistical methods

Ordinary statistical methods were used for calculation of means, medians, standard deviations and percentages. In testing for the significance of differences the following methods were used

The Mann-Whitney U-test for the psychological data.

Student's t test and Chi-square test for the EEG data.

The homogeneous quality of the constructed indices was tested with the Kudor Richardson coefficient (KR_{20}).

The Rorschach test and the Blacky Pictures were factoranalyzed with the Q-factor analysis, (BMDX72), which is an inverted form of R-analysis. Using the Q-technique one gets factor solutions with a clustering of persons having characteristics in common The following procedure was used in the factor analyses. The items were dichotomized and G-indices were computed on the received score-matrices (51). The G-index matrices were computed with the method of principal component and the received factors were rotated with the Varimax method (19) Only persons who had factor loadings of 45 and more were selected for the clusters. The reasons for using the Q-technique were the great number of items and the small number of persons in the study The results of the Q-analysis were considered when selecting items for the correlation analyses.

The Spearman rank correlation coefficient was used for the correlation analyses.

Thirtysix items were selected with regard to the results of the correlation analyses and used in a R-analysis. The rotation programme (BMDX72) used was oblique rotation for simple loadings. The estimated communality was 1 Only items with

factor loadings of .40 or more were selected for the factors.

The statistical analyses thus proceeded according to the following plan

1 Significant differences between diabetic children and their controls were determined. In this context both comparison between means and Q-factor analyses were used

2 In the correlation analyses mainly discriminating items were used.

3 Items with highly significant (illuminating) value in the correlation analyses were selected for a R factor analysis in the search for patterns of interaction.

EEG-technique

The EEGs were taken with a Kaiser electroencephalograph. In most cases 8 channels were used for the EEG and 2 for recording eye movements. The *10–20 electrode system of the International Federation* was used with the customary longitudinal and transverse bipolar derivations. In all recordings one montage with a common reference lead (homolateral ear) was also used. The paper speed was 3 cm/sec, the time constant 0.3 sec and the filter 70 Hz. The procedure was as follows

Recording at rest usually occupied the initial 30 minutes, if the subject did not fall asleep at the outset of the registration. Running notes have been made for the resting EEG regarding the occurrence of drowsiness of the subject. Alerting stimuli such as visual stimuli i.e. eye opening or eye winking, auditory stimuli or fist clenching, were performed several times during the recording.

Hyperventilation was performed for 3 minutes. The subjects were encouraged to draw as deep breaths as possible and a respiration rate of about 20/min was obtained. The recording was continued until 2 min after hyperventilation.

Intermittent photic stimulation was carried out by means of a Kaiser stroboscope (electrical energy = 0.2 joule/flash maximum intensity at 10 flashes/sec 1 8 megalux). The lamp distance was 15 cm. Flashes were produced in the following sequences. *"rising course"* – 4 6 8, 11 15 20 24 flashes/sec each frequency lasting 40 sec, *declining course* – 20 18, 16 15 14 12, 11 10, 8 6 4 flashes/sec, each lasting 20 sec 4 flashes/sec and 24 flashes/sec alternatively for 3 sec on 10 consecutive occasions, and finally 15 flashes/sec 6 times for 5 sec with an interval of 15 sec between each stimulation period.

Sleep records including a run of about 10 to 20 minutes light sleep were kept. When sleep was not achieved spontaneously it was induced by oral administration of barbiturate (mebumal sodium) 7–11 years 80–110 mg, 12 years and more 100–150 mg. The dosage also depended on the weight of the subject and the degree of alertness.

Blood glucose concentration was determined by capillary method (glucose oxidase) before and directly after the EEG recording which in most cases was performed between 1 and 4 p.m. Information had been given in advance in order to avoid the influence on the EEG of hypoglycemia, raised body temperature and fatigue. To avoid hypoglycemia the children were told to eat a full meal one hour before the procedure. Mean blood glucose concentration ±1 S.D before and after the investigation was 271±128 and 248±128 mg per 100 ml respectively. In none of the children hypoglycemia occurred. The EEG-records were analyzed according to the method described by Petersén and EEG-Olofsson (84)

Statistical methods

Ordinary statistical methods were used for calculation of means, medians, standard deviations and percentages. In testing for the significance of differences the following methods were used

The Mann-Whitney U-test for the psychological data.

Student's t test and Chi-square test for the EEG data.

The homogeneous quality of the constructed indices was tested with the Kudor Richardson coefficient (KR_{20})

The Rorschach test and the Blacky Pictures were factoranalyzed with the Q-factor analysis, (BMDX72), which is an inverted form of R-analysis. Using the Q-technique one gets factor solutions with a clustering of persons having characteristics in common. The following procedure was used in the factor analyses. The items were dichotomized and G-indices were computed on the received score-matrices (51). The G-index matrices were computed with the method of principal component and the received factors were rotated with the Varimax method (19). Only persons who had factor loadings of .45 and more were selected for the clusters. The reasons for using the Q-technique were the great number of items and the small number of persons in the study. The results of the Q-analysis were considered when selecting items for the correlation analyses.

The Spearman rank correlation coefficient was used for the correlation analyses.

Thirtysix items were selected with regard to the results of the correlation analyses and used in a R analysis. The rotation programme (BMDX72) used was oblique rotation for simple loadings. The estimated communality was 1. Only items with

Table 4 Mean values for Rorschach responses in diabetic children compared with controls. Values are given for total group boys and girls. Significant differences ($p < 0.05$) denoted by asterisks.

	D	C	Db	Cb	Dg	Cg
Number of answers (R)	16,92	17,59	14,67	17 96	18,81	17,25
W-answers	7,80	7,32	7,00	6,89	8,47	7,69
D-	7,46	7,69	6,44	8,37	8,31	7 13
Dd-	0,64	0,83	0,5**	1,00	0 75	0,96
S	0,80	0,64	0,59	0,44	0,97	0,81
Do	0,08	0,25	0,04	0,15	0,13	0,34
WS	0,9	0,59	1,00	0,70	0,84	0,50
DW	1,36	0 69	1,26	0,52	1 44	0,84
W (cut off) answers	0,59*	0,10	0,48	0,15	0,69*	0,06
F	8,54	9,3	7,56	10,41	9,59	8 41
F	0,73	0 61	0 78	0,37	0,69	0,81
F	1,80*	1,47	1,44	0,70	2,09	2,13
FC	0,93	1,25	0 74	1,33	1,09	1 19
CF	0,98	1,05	0,85	1 11	1,09	1,00
M	1,80	1,85	1,30	1,89	[illegible]	1,81
FM	1,22	1 00	1 15	0,81	1,28	1,16
Small M	0,32	0,20	0,44	0,26	0,22	0,16
FCH	0,31	0,49	0,19	0,26	0,41	0,69
CHF	0,37	0,25	0,26	0,33	0,47	0 19
CH	0,44	0,10	0,33	0,11	0,53	0,09
F(C)	0,39	0,17	0,59	0,19	0,22	0 16
H	[illegible],07	2,41	1 74	2,33	2,34	2,47
Hd	1,61	1,66	0,93	1 41	2,19	1,88
A	6,91	6,37	5,85	6,30	7,06	6,44
Ad	1,25	0,64	0,96	1 74	1,50	1,56
Plants	1,17	1 17	0 78	1,30	1,19	1,06
Object	2,37	1 42	2,81	1 63	3 13*	1,25
Cloth	1 74	0,85	0,85	0,67	1,91	1,00
P	2,63	2,80	2,30	2,85	[illegible],97	2,17
(P)	1 18	0,85	1 41	0,52	1,13	1,13
Orig+	1 46	0,47	1,04	0 81	1,34	0 19
Orig−	0,27	0,02	0,56	0,00	0,09	0,03
Color shock	1 04	0 46	1,22*	0,52	1 16	0,41
Red shock	0,77*	0 15	0,70*	0,15	0,41	0,16
Ch shock	0,89*	0,32	1,11	0,48	0,69*	0,19
Object criticism	1 74	0,18	1,00	0,04	1,53	0,31
Resignation	1,23	0,00	0,59	0,00	0,66	0,00
The evaluating remarks	0,84	0,00	0,41	0,00	0,50	0,00
Uncertainty	1,34	0,07	0,56	0,00	1,13	0,13
Defect answers	1,18	0,08	0,59	0,02	1,03	0,16
Perspective responses	0,34	0,12	0,41	0 19	0,28	0,06
Paranoic	0,63	0,03	0,61	0,03	0,65	0,02
Profile	0,33	0,12	0,26	0,07	0,38	0 16
Confabulation	0,73	0,02	0,41	0 02	0,50	0,01
Figure-background	0,72	0,07	0,19	0,04	0,56	0 09
Emotional lability	0,34	0,05	0,22	0,04	0,44	0,02
Mirror interpretation	0,75	0,27	0,19	0,37	0,44	0 19
Deformation	0,42	0,02	0,26	0,00	0,19	0,03
Perseveration	0,47	0,02	0,33	0 01	0,81	0,04
"Or"-responses	0,82*	0,10	0,87	0 13	0,50	0,06
Inhibition	0,74	0,18	0,56	0,19	0,95	0,16
Black and White as colors	0,79*	0,14	0,68*	0,15	0,91	0,13
Self reference	0,68	0,02	0,07	0,00	0,38	0,03
Penetration	1,37*	0,33	1,44	0,37	1 93	0,78
Barrier	0,93*	1 42	0,96	1 44	1,03	1 41
Oral Answers	1 75	0,06	1,19	0,04	2 32	0,09

N	D	[illegible]	C	59
	Db	27	Cb	[illegible]
	Dg	[illegible]	Cg	[illegible]

Table 5 Item content in Rorschach factors differentiating between diabetic children (D) and controls (C).

Item	Db I	III	IV	XIV	Cb II	VI	Dg IX	X	XI	Cg XII
Number of M-answers 0										
Number of H-answers 0										
Delineation										
Score answers 0	+									
Number of W-answers 10										
WS-answers										
S										
CF										
F(C)										
Black & white as colors										
Object criticism										
Defect-answers										
Blood and fire		+								
The perspective responses										
Color type: left										
A% 40–49										
Color index Colored not c.			+							
F+% 64				+						
Explosion										
Emotionality										
CCh-answers										
Cloud, fog & smoke										
Number of R=0–14, rev										
Number of R 15 30										
F+% 90–99										
F% 30–39										
Asthenic % 30										
RJ = 5–6										
Experience type: ambiequal										
Anatomy response										
Shock										
Number of FM 0, rev										
Number of FM 1 3										
Ch-shock, rev										
FC-answers										
A% 50 70										
Self reference										
F% 80–90										
Experience type: introvert										
Perseveration: rotation										
Perseveration: sticking to a central theme										
Mirror interpretation										
FCh-answers										
Symmetry										
The "or" responses										
Profile answers										
R 1–14										+
F+% 100										
M-answers										
H-answers 5										
Age 6·6–9·5 years	1	0	1	1	0	2	1	0	2	0
9·6–12·5 years	0	2	0	1	0	0	2	0	1	3
12·6–15·5 years	2	1	1	1	6	3	2	3	1	2
Mean duration (in years)	8	7·3	3·4	7·7	–	–	4·1	7·4	3	–

These elements probably are puberty signs as the factor contains children 12.6–15.5 years old.

Factor VI (Cb) has two items in common with factor II. The factor indicates good emotional adjustment and some rigidity.

Factor IX (Dg) implies rigidity and depressive tendencies. The children representing this factor also appear to be egocentric and they have a lack of selfconfidence and lack of emotional stability.

Factor X (Dg) indicates emotional lability and impulsivity combined with introversion and tendencies of ixoid and repetitive perseverations. The factor is related to age and some influence of puberty is possible. The disturbances are profound and probably have developed during several years, as these girls have had their disease for a long time (‾ = 7.4 years).

Factor XI (Dg) indicates neurotic disturbances and inhibition but als compulsory tendencies.

Factor XII (Cg) is similar to factor VI. It indicates good reality adjustment and sociability. It also denotes some asthenic behavior and intellectual ambitions.

Comments

The frequency analysis of the Rorschach responses (Table 4) shows significant differences between the diabetic children and their healthy controls. Many of these differences indicate obvious deviations of the emotional development in the diabetic group. The factor analysis emphasizes these findings and gives the association between certain items and their distribution in the material (Table 5). Thirtysix per cent of the diabetic children are included in the differentiating factors. This is a small number not allowing general conclusions about the group. The factors indicate relatively serious deviations occurring mainly in children with long duration of the disease.

Following are the main differences in the Rorschach responses between diabetic children and controls.

Formal analysis indicates that the diabetic children use background (WS) and separate details (DW) to a greater extent in building up their perceptions than the controls. They seem to have inconsistancy in the structure of their percepts, giving both orig+ and orig–" answers.

"Penetration" scores which are signs of disturbed body image development (35) are rare in the controls but occur in 21 of the diabetic boys and 28 of the diabetic girls. "Barrier" scores occur regularly in healthy controls as an indication of a normal delimination between the individual and his environment. About 50 per cent (15 boys and 16 girls) of the diabetic group lack barrier scores indicating weak body boundaries. High "barrier" scores, appearing in 2 diabetic boys and 6 diabetic girls, can also be a sign of disturbed body image – indicating tendencies to isolation (40).

Responses indicating weakness of the ego structure are found more often in the diabetic group than in the controls. Isolated responses appear in practically all diabetic children, but only 7 children gave these responses consistently.

The increased frequency of "shock" responses indicates psychoneurosis, and this type of answers occurs in all diabetic children except in two boys. The factor analysis gave two factors containing neurotic signs (Db XIV and Dg XI).

Phenomena such as "resignation" and "black and white as colors answer" suggest depressive traits and occur in 10 boys and 9 girls of the diabetic group. Depressive tendencies partly characterize factor Db III and Dg IX. "Defect answers" indicate anxiety and occur in 18 diabetic boys and 18 girls. Pathological responses of these types are infrequent among the controls.

Phenomena which are possible cerebrolesional signs (perseveration, evaluating remarks, inhibition, delimination, uncertainty and "or responses) are frequent in the diabetic group. Many diabetic children (21 boys and 22 girls) have more than two of these answers. Factor Dg X is loaded with these responses.

"Object criticism" occurring in 10 diabetic boys and 28 girls, and "paranoic" answers occurring in 14 boys and 21 girls, can be regarded as signs of aggression and suspiciousness towards the environment.

The Blacky Pictures test

Table 6 shows the number of spontaneous stories scored as "strong" (13) in the two investigated groups. The number of "strong" stories given by the diabetic group exceeded that given by the controls for all cartoons except two: cartoons II and IV. Some examples of the themata of the spontaneous stories are given in Table 7.

The Q-factor analysis of the questions of the inquiry and the cartoon preferences gave 15 factors for the boys and 18 for the girls. The final

Table 6. Number of spontaneous stories of the diabetic and control children scored "strong" according to G Blum, Blacky Pictures.

Cartoons		Dimensions	Diabetic boy	girls	Control boys	girl
I		O al Eroticism	16	8	1	1
II		Oral Sadism	0	0	0	0
III		Anal Sadism	4	5	1	0
IV		Oedipal I tensity	27	15	14	16
V		Masturbation Guilt	7	17	2	2
VI		Castration Anxiety	9	15	2	4
VII		Posit Identificatio	8	12	0	0
VIII		Sibling Rivalry	7	11	1	2
IX		Guilt Feelings	7	5	0	1
X	+	Pos. Ego Ideal, Love	10	12	0	0
XI	+	Pos. Ego Love Object	20	15	4	3

\+ On cartoons VII X and XI numbe of not strong stories are counted because here not [illegible] ng indicates unfavorable adjustment.

Table 7 Interesting themata in the spontaneous stories of the Blacky Pictures.

Cartoon		Number of store Db	Dg	Cb	Cg
I	B. will stay all his lif eating	14	5	1	1
IV	B is isolated	5	6	1	0
	The mother is tired	7	8	0	0
	B. is longing for his mother's affection	19	10	4	12
	B is longing for his father s affection	27	15	14	19
	B. prefer t be together with the whole family	0	2	13	16
	Nobody wants B.	5	6	0	0
V	B. is making his toilet, which the parents like	20	15	25	30
	B is good dog keeping himself clean	7	17	2	2
VI	B. knows that it is his turn	9	14	2	4
	T is going to commit suicide	0	1	0	0
VII	B has found peculiar dog, which he doesn t need to be afraid of	8	12	0	0
	B tells the toy dog t imitat him	21	20	27	32
VIII	B is jealous but he tries to find out why he does not get any attention	20	21	27	32
	B. is longing for revenge and fight	5	8	0	0
	B is running away from home	2	3	0	0
IX	B feel guilty and want to change his behavior so that the parents will forgive him	20	27	27	31
	B is scared to death	7	5	0	1
X	B dreams about being grow up handsome and capable	12	15	26	31
	B. dreams about being grow p ugly and stupid	10	9	1	0
	B. dreams about being big enough t fight his parents	5	8	0	0
XI	B. dreams about his girlfriend	7	12	20	28
	B dreams that he is becoming girl instead of boy	6	0	0	0
	B. dreams about his mother	14	8	4	4
	B. is very depressed when he is dreaming of the future	0	7	0	0

Table 1 Correlations between the psychological assessment and peri- and postnatal events.

	Head trauma			Abnormal delivery			Birth weight			Neonatal symptoms			[illegible]		
	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
WISC	04	0	0	16		05	01	02	04	17	3	14	16	37	05
Neurotic I	03	34		13	0	2	1	33	20	17	15	24	02	05	−03
Cerebrolesional I	11	20	6	20	13	30	19	09	6	03	0	08	−05	3	11
Percept. d. ... I	0	45	18	1	4	3	11	15	11	08	16	09	1	16	−2
Maladjustment I	.05	08	15	20	6	45	4	32	4	10	25	05	16	13	18
Paranoid risk	11	20	11		08	45	03	19	09	28	2	10	09	10	18
Object relations	16	4	0	4	1	45	0	11	09	07	10	10	1	03	1
Emotional lability	1	..	49*	1	20	13	05	10	13	17	17	19	14	19	09
Aggression	.0	03	01	1	34	1	12	08	17	09	05	16	07	05	13
Oral preoccupation	11	14	10		3	41	10	34	11	12	19	15	11	13	19
Penetration	18	30	0	13	34	05	06	05	01	15	03	31	07	09	19
Barrier	.06	9		10	11	09	09	01	16	18	0	6	0	15	07
Loneliness	13	0	14	10	08	10	01	28	08	05	11	1	4	10	3
Identity I	17	05	29	06	01	1	05	07	02	15	13	8	1	17	09

* $p < 0.05$

T total material (n 59)
Db boys (n 27)
Dg girls (n 32)

	n=59	n=27	n=32
Confidence level .01	34	53	48
.05	6	40	36

Table 18. Correlations between the psychological assessment and interview data.

	Schoolproblems			Peer problems			Aggression			Paroxysmal headache and or abdominal pain			Anxiety index			Worry for the future		
	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
WISC	.22	.26	18	18	.53	12	06	06	13	.09	29	10	20	11	26	22	23	.25
Neurotic I	19	19	41	06	18	18	32	.51	.35	– 10	10	26	48	67	36	34	.59	24
Cerebrolesional I	26	19	30	23	18	.25	21	40	10	13	21	03	14	22	07	17	26	20
Perceptual dist I	15	11	23	12	21	– 22	09	10	06	20	.29	17	06	02	06	07	28	17
Maladjustment I	.29*	36	39	10	07	11	04	33	07	.27	.30	37	27*	32	40	05	45	11
Paranoid Traits	22	10	27	12	.03	15	20	12	21	– 01	13	14	13	[illegible]	10	.25	41	28
Object criticism	.27	41	29	14	09	17	14	09	12	03	03	12	12	.08	10	10	17	17
Emotional lability	.04	05	.08	27	41	37	11	16	05	06	15	04	6	30	24	15	36	07
Aggressivity	.02	35	.39	39	41	46	41	44	39	19	16	14	25	37	12	15	29	06
Oral Preoccupation	16	14	.22	14	24	[illegible]	15	15	14	– 01	13	– 15	.09	– 08	09	14	[illegible]	20
Penetration	37	41	40	36	40	40	26	.39	[illegible]	02	02	.02	29	.39	36	.36	.29	.53
Barrier	.27	.34	[illegible]	23	– 39	.23	04	17	18	– 15	– 08	15	.25	– 40	– 29	–.09	13	– 23
Ego weakness	.02	18	14	26	27	26	02	03	02	.01	01	–.05	03	.08	09	08	.09	26
Identity I	.01	10	10	04	11	07	10	02	.20	–.05	17	– 15	34	42	40*	38	.53	41

$p < 0.05$

T	total material	(n 59)		
Db	boys	(n 27)		
Dg	girls	(n 32)		
		n=59	n=27	n=32
Confidence level	.01	.34	.53	48
	05	26	40	.36

The attitudes of the environment to the diabetic child

As mentioned above all 58 mothers but only 43 fathers participated in the interview. The attitudes of the mothers and the fathers towards the disease and child rearing are summarized in Tables 19, 20 and 21. All fathers interviewed were of the opinion that the mother had the responsibility for the diet, and only three of the fathers concerned themselves with the insulin injections. Their attitudes towards diet and injections therefore have been disregarded. The attitudes of the control mothers to child rearing are given in Table 21.

Comments

Most parents described their first reaction to the information about their child's diabetes as a strong emotional experience, often using the word *"despair" or "shock". The only parents who could* display a composed reaction were those who either had relatives with the disease or who worked in a hospital. This points to the importance of objective information about the disease from the very beginning.

The daily care of the diabetic child burdens the mother who in the majority of the cases has definite difficulties in coping with the disease. It is frequently difficult for mothers to follow the dietary prescriptions. Few children (4 boys and 5 girls) do not need any help with the insulin injections, and as a rule, the mothers find or found the necessity to give their own children injections a disagreeable experience.

In extraordinary situations the fathers take more responsibility than in the daily routine but the mothers still seem to bear the brunt of the burden. In some cases there is differing opinion between the parents as to who is given the prime care. Both parents, as a rule, realize that the disease will influence the future professional plans *of the child, and seem to be more concerned* about the boys in this respect.

In comparison with parents of the control group

Table 19 The attitudes of the mothers towards the diabetic disease

Question (see Appendix 1)	Type of answers		Db No	%	Dg No	%
1 Reaction to first information	Composed	(1)	2	7,4	3	9,4
	Despair	(2)	6	22,2	8	25,0
	Shock	(3)	19	70,4	21	65,6
2 Coping with the disease	Easily adapted	(1)	1	3,7	8	25,0
	Adapted with difficulty	(2)	14	51,9	20	62,5
	Not adapted	(3)	12	44,4	4	12,5
3 Difficulties in following dietary prescriptions	No	(1)	5	18,5	6	18,8
	Yes	(2)	22	81,5	26	81,2
4 Attitude to insulin injections	No difficulties	(1)	5	18,5	3	9,4
	Got used	(2)	9	33,3	8	25,0
	Disagreeable	(3)	13	48,2	21	65,6
5 Influence on choice of profession	No	(1)	2	7,4	8	25,0
	Yes	(2)	25	92,6	[illegible]	75,0
6 Opinion of obtained information about the disease	Good	(1)	8	29,6	12	37,6
	Fair	(2)	7	25,9	10	31,2
	Bad	(3)	12	44,5	10	31,2
7 Responsibility in extraordinary situations	The interviewed		16	59,3	17	53,1
	Wife/husband		3	11,1	0	
	Both		8	29,6	15	46,9
14 Member of the diabetic association	Yes	(1)	12	44,4	16	50,0
	No	(2)	15	55,6	16	50,0
15 Activities together	Yes	(1)	16	59,3	15	46,9
	No	(2)	11	40,7	17	53,1
16 Physical exercise together with the child	Yes	(1)	16	59,3	15	46,9
	No	(2)	11	40,7	17	53,1

Table 20. The attitudes of the fathers towards the diabetic disease and the rearing of the child

Question (see Appendix 1)	Type of answers		Db No	%	Dg No	%
1 Reaction to first information	Composed	(1)	2	10,0	3	13,0
	Despair	(2)	10	50,0	10	43,5
	Shock	(3)	8	40,0	10	43,5
5 Influence on choice of profession	No	(1)	3	15,0	7	30,4
	Yes	(2)	17	85,0	16	69,6
6. Opinion of obtained information about the disease	Good	(1)	7	35,0	5	21,8
	Fair	(2)	7	35,0	7	30,4
	Bad	(3)	6	30,0	11	47,8
7 Responsibility in extraordinary situations	The interviewed		3	15,0	–	–
	Wife/husband		8	40,0	13	56,6
	Both		9	45,0	10	43,4
8 Consequent rearing	No	(1)	13	65,0	13	56,6
	Yes	(2)	7	35,0	10	43,4
9 Special instruction	0–2	(1)	16	80,0	13	56,6
	More than 2	(2)	4	20,0	10	43,4
10. Protection from unpleasant experiences	No	(1)	9	45,0	8	34,8
	Yes	(2)	11	55,0	15	65,2
11 Knowledge about possibilities and limits	No	(1)	7	35,0	15	65,2
	Yes	(2)	13	65,0	8	34,8
12. At which age away from home	10–12 years	(1)	10	50,0	12	52,2
	Later	(2)	10	50,0	11	47,8
13. Prefer to have the child at home	No	(1)	10	50,0	13	56,6
	Yes	(2)	10	50,0	10	43,4
14 Member of the diabetic association	Yes	(1)	12	60,0	12	52,2
	No	(2)	8	40,0	11	47,8
15. Activities together	Yes	(1)	11	55,0	6	26,1
	No	(2)	9	45,0	17	73,9
16. Physical exercise together with the child	Yes	(1)	10	50,0	13	56,6
	No	(2)	10	50,0	10	43,4

Table 21. The attitudes of the mothers towards the rearing of the children.

Question (see Appendix 1)	Type of answers		Db No	%	Dg No	%	Cb No	%	Cg N	%
8. Consequent rearing	No	(1)	25	92,6	19	59,1	22	81,5	20	62,5
	Yes	(2)	2	7,4	13	40,6	5	18,5	12	37,5
9 Special instructions	0–2	(1)	20	74,1	16	50,0	22	81,5	14	43,7
	More than 2	(2)	7	25,9	16	50,0	5	18,5	18	56,3
10. Protection from unpleasant experience	No	(1)	6	22,2	9	28,1	7	25,9	8	25,0
	Yes	(2)	21	77,8	23	71,9	20	74,1	24	75,0
11 Knowledge about possibilities and limit	No	(1)	17	63,0	19	59,4	8	29,6	7	21,9
	Yes	(2)	10	37,0	13	40,6	19	70,1	25	78,1
12. At which age away from home	10–12 years	(1)	9	33,3	12	37,5	19	70,1	27	84,4
	Later	(2)	18	66,6	20	62,5	8	29,6	5	15,6
13. Prefer to have the child at home	No	(1)	9	33,3	13	40,6	22	81,5	21	65,6
	Yes	(2)	18	66,6	19	59,1	5	18,5	11	34,4

parents of diabetic children seem to have the same general attitude to child rearing. The majority of the parents find it difficult to be consistent or do not try to be so. The attitude towards the boys and the girls differs in this respect. More consistency seems to be used in rearing the girls who also are given more instructions when leaving home. The parents of diabetic children take neither more nor less interest in their children than do the parents in the control group. In this context it is of interest to note that only about 50 per cent of the parents take physical exercise together with their diabetic child. About 15 per cent of the fathers and 10 per cent of the mothers take physical exercise by themselves despite the fact that the child would benefit from joining them.

In one respect parents of diabetic children differ from those in the control group. Answers indicating an overprotecting attitude are significantly more frequent among parents of diabetic children.

The interview with the teachers revealed that the parents usually had informed the teacher about the child's disease early. In most cases the teacher regarded the contact with the parents as satisfactory.

Correlations between the psychological assessment and the attitudes of the parents

The correlations between the psychological assessment and the attitudes of the parents are given in Tables 22 and 23, which also show the relations between social group and attitudes.

Comments

Because of the limited number of fathers participating in the interview and their limited role in the daily care of the diabetics the main interest should be directed to the influence of the mothers attitudes. The attitudes of the parents, especially the mother seem to be of great importance for the genesis of personality disturbances in the diabetic children. This influence appears to be at least as important as the effect of the disease *per se*.

The attitudes of the parents are related to their social status. The dominating feature of the correlation analyses is the close association between the development of body image, ego structure and the identification processes, and maternal attitudes. To a lesser degree these attitudes are related to emotional lability, aggressivity and paranoic reactions.

A wish to have the child at home is correlated to cerebrolesional and perceptual disturbances in the child. Since hypoglycemic convulsions had occurred in many of the children with these disturbances, the attitude is understandable.

The same pattern of associations are found for both parents. However, the results do not allow quantitative comparison between the influence of the father's and mother's attitudes.

Table 22. Correlations between psychological assessment and attitudes of the mothers.

	Reaction to first information			Opinion of obtained information			Influence on daily life			Attitude to insulin injection		
	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
WISC	23	.27	.24	.21	41	05	25	31	39	16	.07	.21
Neurotic I	48	71	42	05	–.06	14	40	41	39	06	12	–.03
Cerebrolesional I	[illegible]	.27	.22	03	– 13	15	02	– 11	22	.05	11	.06
Perceptual disturbance I	16	09	.21	13	– 02	24	.07	29	12	09	.35	– 03
Maladjustment I	.21	.38	17	05	– 17	18	10	– 03	[illegible]	05	17	.00
Paranoid Traits	.06	19	.09	.07	13	12	–.07	–.22	10	.06	18	– 02
Object criticism	.01	–.01	.06	09	[illegible]	13	– 11	– 15	[illegible]	– 03	– 10	– 03
Emotional lability	.27	.27	[illegible]	–.04	14	10	.20	.25	19	30	.21	40
Aggressivity	.03	42	– 16	–.23	02	– 48	– 04	02	.04	.26	.25	42
Oral Preoccupation	16	.31	.09	09	[illegible]	15	06	01	.08	05	06	.02
Penetration	*36*	*59*	*.36*	*38*	61	*56*	*40*	40	.59	.08	– 15	04
Barrier	– 15	.08	–.30	– 28	–.32	– 36	–.21	15	.34	01	–.19	19
Egoweakness	.08	.02	17	31	22	43	.01	– 04	16	36	40	.38
Identity I	32	38	39*	.21	02	42	.22	20	.29	11	.07	18
Social group	.21	–.7	15	13	14	– 48	.37	39	39	09	– 06	42

T = total group n *59*
Db = diabetic boy n 27
Dg = diabetic girls n 32

	T	Db	Dg
Confidence level .01	.34	.53	48
.05	.26	40	.36

Table 23 Correlations between psychological assessments and attitudes of the fathers.

	Reactions to first information			Opinion of obtained information			Consistent rearing			Prefer to have the child at home		
	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
WISC	.22	.50	.02	32	19	47	15	– 29	13	04	[illegible]	.02
Neurotic I	26	27	.26	09	17	27	15	14	15	11	.08	15
Cerebrolesional I	06	13	.04	27	27	24	07	21	05	29	.09	.52
Percept. dist. I	12	07	15	18	07	31	14	48	01	31	.05	47
Maladjustment I	08	08	.07	27	08	29	05	09	08	27	.32	.56
Paranoid Trait	.08	20	08	[illegible]	04	28	04	02	03	24	12	43
Object criticism	06	06	09	20	09	21	08	04	02	27	–.04	45
Emotional lability	.06	.24	– 18	07	06	16	10	01	08	01	.23	– 04
Aggressivity	– 02	10	– 12	09	13	04	27	47	01	13	04	– 18
Oral Preoccupation	06	21	.09	21	11	34	.05	31	09	.36	23	.52
Penetration	18	06	46	17	06	27	15	.04	40	20	.38	– 05
Barrier	34	[illegible]	31	01	.07	[illegible]	27	25	28	24	.09	–.29
Egoweakness	32	38	.30	27	27	28	17	18	49	03	12	07
Identity I	.26	18	32	08	.08	23	10	10	10	.08	.26	[illegible]
Social group	42	50	37	13	[illegible]	10	42	27	34	09	.09	– 14

* $p < 0.05$

T total material (n 43)
Db boys ([illegible] 0)
Dg girls (n 23)

	n=43	n 20	n=23
Confidence level .01	41	.62	.58
.05	.31	48	44

Attitude to diet			Consistent rearing			Prefer to have the child at home			No activity together			No physical exercise together		
T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
[illegible]	42	45	11	−.06	.21	.27	15	40*	.35	40	41	.56	.6	.50
.27	.22	.30	15	.21	.07	14	−.05	.26	13	−.05	.30	.02	− 13	.08
.25	.22	.30	.24	−.05	13	.32	46	.33	−.03	− 17	19	.18	.06	19
.23	.34	.22	.15	−.12	.11	.28	−.08	.36	.11	18	13	[illegible]	11	13
17	18	17	.07	− 49	18	.2	− 17	40	.06	− 13	15	.11	−.5	.07
16	.30	17	.24	−.01	14	16	10	.23	.09	12	17	.39	48	.36
14	−.03	.21	10	.05	15	.25	.22	.34	−.08	.09	.17	.09	− 13	.05
.24	.20	.30	.20	.28	.02	.18	15	.34	.04	.05	10	.39	40	39
.16	.23	.09	.21	.32	.09	− 14	.00	−.25	−.04	−.05	.01	− 02	− 1	.0
14	−.02	19	12	.23	.09	−.1	13	.21	−.08	.15	15	.13	.05	14
19	.04	.32	.27	.3	.28	.28	−.6	40	1.00	1.00	1.00	.36	.33	.36
17	− 16	− 18	−.08	.02	− 11	− 12	− 19	−.08	− 13	− 1	− 15	−.04	.0	10
.34	46	.36	−.02	.02	−.12	12	.05	.20	.27	.33	.36	1.00*	1.00*	1.00
19	1	18	−.06	−.05	−.07	.13	[illegible]	16	13	17	.08	.05	11	.0
.29*	.42*	46	−.30	− 41	−.26	−.01	−.29	.22	1	.17	.03	46	40	.50

No activity together			No physical exercise together		
T	Db	Dg	T	Db	Dg
.33	.61	.02	43	.67	18
− 10	13	.08	.01	16	10
− 12	17	.26	.03	.04	.08
[illegible]	.02	.26	09	−.05	11
16	12	32	.07	.06	.09
16	.07	.24	04	12	.06
[illegible]	13	.17	.07	17	.06
01	.28	− 14	.24	[illegible]	40
18	−.09	.25	.03	.04	.03
15	.03	.21	.01	.06	.02
19	37	01	.01	.04	.06
1.00	1.00	1.00*	.53	.53	.52
.33	.29	.38	.55	34	74
.24	.25	.25	.07	04	10
49	.63	32	[illegible]	.40*	58

The electroencephalographic investigation

Four girls refused to participate in the EEG examination which as a result was only performed on 55 of the diabetic children – 28 girls and 27 boys.

The following EEG patterns, all occurring in the "controls" (C') varying with age and sex have been analyzed more in detail

At rest – alpha frequency alpha amplitude incidence of beta activity incidence of non rhyt mic low frequency activity slow posterior rhytms and polyphasic potentials

At hyperventilation (HV) – incidence of diffuse rhytmic responses;

At intermittent photic stimulation (IPHS) – low frequency activity

Incidence of paroxysmal activity at rest, at HV during sleep (or drowsiness) and IPHS

Incidence of the fourteen and six per second positive spike phenomenon (14-6-PS)

The various patterns are characterized in Table 24 and the results of the comparison between the diabetic group and the age matched "controls" are given in the table or in the text.

Drowsiness, i.e. reduced alertness during extensive segments of the record was noticed in 14 of the diabetic children (25.5 %). Spontaneous sleep occurred in 29 children (53 %), which is significantly more than among the "controls" (29 %).

EEG-findings at rest

The alpha frequency varied between 8 and 11 Hz. As in the "controls" it increased with age but it was significantly lower in the diabetic group than in the "controls" The alpha amplitude also was significantly lower in the diabetic children. Ample amount of beta activity was found in 6 diabetic children (10.9 %) which is a significantly higher incidence than in the "controls" Its amplitude varied between 5 to 20 microvolt (mean value = 8.6 S.D = 3 7). The beta amplitude was not measured regularly in the "controls" and therefore a statistical comparison could not be done

Non rhytmic low frequency activity occurred in 38 % of the diabetic children and 16 9 % of the "controls" a statistically significant difference In five diabetic children this type of pattern appeared episodically at rest, an occurrence which never could be demonstrated in the "controls" and therefore must be regarded as abnormal

The incidence of rhytmic low frequency activity – slow posterior rhytms and polyphasic potentials – did not differ significantly in the two groups. Polyphasic potentials were counted per 100 sec. The mean values for the two groups did not differ significantly The percentage of cases with less than 24 polyphasic potentials per 100 sec was also the same in the two groups. However the median value in the diabetic group was 10 and in the "controls" 5

EEG responses to HV

The analysed response – diffuse 2–7 Hz activity – appeared in significantly fewer diabetic children (30.9 %) than in the "controls" (61 7 %).

EEG responses during IPHS

The incidence of low frequency activity during IPHS was significantly higher in the diabetic group than in the "controls" (30.9 % and 7.3 %).

Paroxysmal activity

Paroxysmal activity occurred at rest in 2.7 % of the "controls" and in 10.9 % of the diabetic children (6 cases), a significant difference which accounts for the difference in total paroxysmal activity between the two groups. In the "controls" paroxysmal activity increases considerably during sleep (drowsiness) or during IPHS (incidence 8.8 % and 9.0 % respectively). The effect of sleep is more pronounced before the age of 10, after 10 the effect of IPHS seems to dominate The effect of IPHS is more pronounced in the girls. In the diabetic group paroxysmal activity during IPHS occurred only in the girls, while at rest and sleep the activity was more common in boys.

The above mentioned episodic low frequency activity appeared in five of the six diabetic children with paroxysmal activity at rest. Although not diagnostic taken alone the finding of an increased amount of paroxysmal phenomena reinforces the pathological character of these EEG records. In Tabel 25 clinical and psychological data common to the five children with pathological EEG:s are given.

Table 24 Comparison between electroencephalographic findings in diabetic children and "controls" (C)

Type of EEG-pattern	General characteristics		Mean ± S.D./incidence	
Alpha-frequency (Hz)	8–13 Hz. Increasing with age higher in girls.	D	9,4± 0,7	
		C	9,6± 0,3	
		t-value	2,18	$p < 0.05$
Alpha-amplitude (µV)	Max. at 6–9 years of age	D	47,7±16,1	
		C	57,2± 4,2	
		t-value	4,32	$p < 0.0001$
Beta-activity (mixed or ample amount)	14–30 Hz.	D	6/55 (10,9 %)	
		C	6/491 (1,2 %)	
		X^2	21,59	$p < 0.00001$
Non-rhytmic low frequency activity (Slight to moderate increase incidence)	(1–)–4–7 Hz. Decreasing incidence after 8–9 years of age	D	21/55 (38,2 %)	
		C	81/491 (16,9 %)	
		X^2	15,31	$p < 0.0001$
Slow posterior rhythm (incidence)	2,5–4,5 Hz. Max incidence at 5–7 years of age. Before the age of 8 more frequent in girls. Posterior. Location.	D	14/55 (25,5 %)	
		C	78/491 (15,9 %)	
		X^2	3,23 (n.s.)	$p < 0.1$
Polyphasic potentials (No per 100 sec)	2–4 Hz. Initial positive phase, following slow negative wave with superposited alpha-activity Decreasing incidence with age. Posterior. Location.	D	11,9±10,5	
		C	8,8± 2,8	
		t-value	1,42 (n.s.)	$p < 0.2$
Diffuse rhytmic response to hyperventilation (incidence)	(2–)–3–7 Hz. Max incidence at 9–12 years of age.	D	17/55 (30,9 %)	
		C	303/491 (61,7 %)	
		X^2	–19,34	$p < 0.00001$
Low frequency activity during intermittent photic stimulation (incidence)	(2–)–4–7 Hz. Max incidence at 5–9 years of age. Posterior or diffuse. Location.	D	17/55 (30,9 %)	
		C	36/491 (7,3 %)	
		X^2	22,36	$p < 0.00001$
Paroxysmal activity (except 14-6-PS) (Incidence)	Spikes on sharp waves bursts of delta and/or theta activity with amplitudes exceeding at least twice that of the background activity. Focal or diffuse location. Max incidence at 6–10 years.	D	18/55 (32,7 %)	
		C	71/491 (14,5 %)	
		X^2	12,10	$p < 0.001$
14-6-PS Max incidence at 13 years there after declining slowly	13–15 and 5.5–7 Hz. "Positive" spike phenomenon. Temporal. Location.	D	9/56 (16,4 %)	
		C	82/370 (21,6 %)	
		X^2	0,96 (n.s.)	$p < 0.5$

Hz. cycles per second, µV microvolt, D diabetic group C = controls"

t 1,96 $p < 0.05$ X^2 3,84 $p < 0.05$

Table 25 Diabetic children with pathological EEG Relevant electroencephalographic, clinical and psychological findings.

Case	Sex	Age	Birth-weight	Episodic low frequency	Paroxysmal activity at rest: Spikes/Sharp waves	Paroxysmal activity at rest: Paroxysmal slow activity	Duration of disease	Degree of control	Hypoglycemic convulsion (N of attacks)	Paroxysmal abdominal pain/headache	Tics nail-biting etc.	WISC (stanine)	Maladjustment Index (Bender)	Aggressivity (Rorschach)
7	M	9·02	4350			( )	6·04	2	2			7	3	+
11	M	10·10	4000			+2	6.00	2	2	+	+	8	4	+
14	M	12 01	4070				6·05	2	1	+	+	7	3	
6	F	10·00	3870		( )	1	3·06	3	3	+	+	7	3	+
31	F	14 00	3150			1 2	7·09	3	1	+	+	5	3	+

M male unequivocal 1 add. parox. act. during IPHS
F female ( ) equivocal 2 add. parox. act. during sleep

The incidence of 14-6-PS did not differ significantly in the two groups, appearing in 16.4 per cent of the diabetic children and 21.6 per cent of the controls. A "totally normal" EEG e.g. a record without increased amount of low frequency activity and/or paroxysmal phenomena was found in 22 diabetic children or 40 per cent of the group.

In normal children many of the analysed variables are age and sex dependent (23). Dividing the two groups according to age 7–11 years and 12–15 years, and repeating the statistical analysis regarding age and sex did not change the overall picture of the differences between diabetic children and "controls".

Comments

Electroencephalographic abnormalities indicating obvious focal or diffuse cerebral lesion did not occur in the diabetic group. However, in five of the children the EEG records were classified as definitely pathological due to episodic low frequency activity and paroxysmal activity at rest. These five children displayed several features in common which are summarized in Table 25. They all had had hypoglycemic convulsions, which had occurred one to three times. All had suffered from diabetes mellitus for a long time. The psychological assessment gave the picture of gifted children, emotionally disturbed, aggressive and with a critical or paranoic attitude. Vegetative symptoms such as recurrent headache and abdominal pain and behavior deviations such as tics, excessive nailbiting etc. were found in all five children. It is interesting to note that these children did not score on cerebrolesional or perceptual disturbance indices. Nor did the better than average performance on the WISC with a coherent test profile indicate a cerebral lesion. Consequently neither the EEG records, nor the psychological assessments gave definite signs of brain damage in these five children. The hypoglycemic episodes however constitute an evident feature of the group.

The incidence and/or character of several EEG patterns differed significantly between the diabetic children and the "controls". These differences might depend on a delay in the development of the EEG in diabetic children concomitant to a general noxious effect of the metabolic disturbances on the function and maturation of nerve cells.

It should also be observed that the diabetic children did not fulfill all the criteria of normality set up for the "controls" but presented deviations during the peri- and postnatal period. These events may be responsible for some of the EEG deviations found in the diabetic group.

From a genetic point of view the diabetic group constitutes a *selected* group of children, in which delayed EEG (brain) maturation might be a constitutional feature. The psychological assessment, however, did not demonstrate signs of an immature personality structure.

The lower incidence of diffuse responses to hyperventilation in the diabetic children compared to the "controls" is in accordance with the reported effect of hyperglycemia on the EEG (20). A significant correlation between blood glucose concentration and lack of diffuse response to hyperventilation was found in the present investigation.

The higher incidence of spontaneous sleep in the diabetic group might point to the fact that diabetic children has an increased potentiality for falling asleep, which fits their increased tendency for drowsiness, as seen in the EEG records at rest. The finding may also have a very simple explanation: for most of these children the EEG investigation was a well known procedure, not provoking curiosity or anxiety.

Correlations between the electroencephalographic patterns and the psychological and clinical data in the diabetic child

The EEG patterns of the diabetic children differing significantly from those of the "controls" were correlated to the results of the psychological assessments, Table 26. In this table only those EEG patterns which gave one or more significant correlations are included. Although the incidence of the 14-6-PS pattern in the two groups did not differ significantly, this pattern was included because of its well documented association [illegible] behavior disorders and specific personality [illegible] (45 46 64 79).

The most conspicuous result of the [illegible] analysis is the number of correlations [illegible] *alpha frequency and indices/item* [illegible] brolesional traits and perceptual [illegible] disturbances found in the [illegible]

interesting to note the significant correlation between high alpha frequency and good mental capacity in the boys. Lack of diffuse response to hyperventilation correlates significantly to perceptual disturbances and maladjustment indices as well as to mental capacity. In the boys significant correlations are found between paroxysmal activity and perceptual disturbances, and between 14-6-PS phenomena and neurotic traits as well as aggressivity. In the evaluation of these correlations, however, the low incidence of 14-6-PS phenomena in the diabetic groups (6 boys, 3 girls) must be considered.

In Table 26 the EEG findings are correlated to those psychological data which are used throughout the correlation analyses. Further analyses reveal a more extensive association between EEG patterns and responses on the personality tests. In Table 27 some Rorschach and Bender items are given that are significantly correlated to EEG pattern. These items have not been included earlier in the correlation analysis, neither isolated nor in indices.

In Table 28 the correlation between EEG patterns and some symptoms commonly seen in child psychiatry practice are shown. School problems are related to low alpha frequency, lack of diffuse response to hyperventilation and to paroxysmal activity, while difficulties with peers do not seem to be associated with deviating EEG-patterns. Emotional disturbances revealed by the interviews (anxious behavior in the girls, and aggression in the boys) and by the projective techniques are correlated to the same EEG patterns, (Tables 26 and 28).

The correlations between EEG-patterns and clinical somatic data are given in Table 29. Although it is difficult to find a general trend in the distribution of the significant correlations, frequent hospitalizations, hypoglycemic convulsions and low birth weight seem to be the most important events associated with EEG deviations.

During the EEG procedure seven children did not fall asleep despite of sedation. This fact correlated significantly to high intelligence, paranoid traits and perceptual disturbances.

Comments

Electroencephalography is used to a great extent in clinical work. Normal patterns are now well established for all age groups (23, 48). The association between organic cerebral disorders and different abnormal EEG patterns is well documented and used in diagnostic work. Alterations of the EEG pattern in mental diseases are also well known. The association between EEG patterns and psychological characteristics is less well investigated. Existing reports mainly concern adults, and reports from work with children are rare. Walter (108) has reported a correlation between theta activity and temper tantrums in children, and Stevens et. al. (99) demonstrated a relation between EEG abnormalities and behavior disorders. A comparison between these investigations and the present study is difficult, because of different terminology. On the whole, the nature and significance of the normally occurring EEG patterns in children are still comparatively unknown. The interpretation of the correlations between EEG deviations and personality traits obtained in the present investigation must therefore necessarily be done with caution.

In the past, attempts were made to correlate personality types with the alpha rhythm. Lemere (70) found a high alpha index associated with schizoid personality. A relationship between low alpha frequency and anxiety and depression has been demonstrated in adults (100, 106). Frey & Forssman (42) found low alpha frequency also in delinquent adolescents. In the present investigation of diabetic children low alpha frequency is that EEG pattern which gives most significant correlations to personality traits, Table 26. A low alpha frequency is correlated to different emotional disturbances. Besides, there is a distinct relation between cerebrolesional traits including perceptual disturbances and a low alpha frequency. This disturbed perception may give learning and memorizing disability causing school difficulties. A perceptual disturbance can also lead to difficulties in understanding emotional attitudes of the environment and thus weaken the basal steering of behavior through social reinforcement (87). Therefore it is of interest to notice the correlation between low alpha frequency and identification problems seen in the diabetic girls.

The correlation between low alpha frequency and cerebrolesional and perceptual disturbances indicates a lesional factor contributing to the deviation of this EEG pattern. This conclusion is

Table 26. Correlations between electroencephalographic and psychological data.

	Alpha-frequency			Alpha-amplitude			Diffuse response t hyperventilation			Total paro ysmal activity			14 – 6 – PS		
	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
WISC	.28	43	12	01	15	.05	–.28	–.23	– 39*	–.01	15	– 17	– 08	– 13	–.06
Neurotic I	15	04	77	02	– 08	15	–.02	.38	22	01	–.01	.03	.28	40	14
Cerebrolesional L	.20	14	.88	.23	07	.34	–.25	–.25	–.25	01	10	–.09	11	23	06
Perceptual d sturbance I	34	41	94	13	02	.26	40*	–.33	–.55	.28	.50	.03	14	.06	22
Maladjustment I	[illegible]	.28	92	25	.20	.38	.28	– 42	– 12	21	.35	13	11	.28	02
Paranoid Trait	.05	18	97	13	40	11	09	–.02	19	16	[illegible]	– 09	– 02	16	–.22
Object Crit ism	20	08	96	25	24	.21	16	17	15	.04	.01	03	– 17	–.04	– 26
Emotional Lability	15	41	19	08	15	10	03	.27	05	.05	– 27	.01	07	.28	.21
Aggressivity	.27	31	.28	.06	13	.24	.02	.01	.03	–.05	– 01	– 09	13	42	–.02
Orality	27	26	[illegible]	03	25	15	12	10	31	19	11	26	01	.20	–.20
Penetration	11	29	06	12	20	[illegible]	11	07	14	.07	02	.08	– 06	– 12	–.02
arrier	11	10	31	14	23	21	06	.25	28	01	11	08	– 05	– 10	03
o Weakness I	.21	.35	23	12	26	17	21	.23	19	.09	.23	.08	09	– 16	35
nxiety I	15	.05	39	03	10	07	18	.04	.31	.04	21	13	07	28	– 24

* $p < 0.05$

T total mat rial (n 55)
Db boy (n 27)
Dg girl (28)

	n=55	27	28
Confidence level .01	.36	.53	.52
05	.27	40	.39

Table ?7 Significant correlations between electroencephalo ta ›hic patterns and some items in the Rorschach and Bender tests.

	Alpha frequency		Diffuse response to hyperventilation		14 – 6 – PS		Total paroxysmal activity	
Rorschach	Cloth answers	.53 (Dg)	F answers	–.38 (Dg)	Cloth answers	65 (Db)		
	I (C) answers	31 (T)	Mirror inter pretation	– 44 (Db)	Mirror inter pretation	.33 (T)		
	Orig answers	.30 (T)						
	Mirror inter pretation	43 (Dg)						
	'Eigraberle-hung	61 (Dg)						
Bender (Hutt)	Curvature difficulties	34 (T)	Perceptual rotation	.31 (T)	Overlapping difficulties	.35 (Db)	Crossing diff	.50 (Db)
			Overlapping difficulties	40 (Db)			Change in angu-lation	.36 (Dg)
			Curvature difficulties	46 (Dg)				
Bender (Pascal-S (tell))			Perseveration	.27 (T)				

Table 28. Correlations between electroencephalographic patterns and psychiatric symptoms.

	Alpha frequency			Alpha amplitude			Diffuse response t hyperventilation			Total paroxysmal activity			14 – 6 – PS		
	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
Tics, nailbiting, stuttering, etc.	.01	19	12	.09	–.28	02	.01	–.04	03	–.07	14	– 86	14	– 25	.02
Paroxysmal abdominal pain or headache	.05	25	.06	06	13	.07	24	.54	08	37	.54	30	.02	.39	– 12
School difficulties	.27	.23	31	13	.81	.22	14	– 40	16	.29	.35	25	18	12	.31
Difficulties with peers	.07	.03	11	.09	.27	10	– 02	–.07	03	.09	.09	10	.01	–.06	.09
Anxiety index	.27	.08	.81	04	06	– 20	–.20	–.38	.01	.09	– 24	.03	14	.22	08
Aggression	19	.33	.03	15	.03	.24	11	.07	13	–.02	.07	– 11	14	40	– 17

p < 0.05

T	total material	(55)
Db	boy	(27)
Dg	girls	(28)

	n=55	n=27	n=28
Confidence level .01	.36	.53	.52
.05	.27	40	.39

Table 29 Correlations between electroencephalographic patterns and relevant clinical data.

	Alpha frequency			Alpha amplitude			Diffuse response to hyperventilation			Total paroxysmal activity			14 – 6 – PS		
	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
Age t onset	23	27	17	12	31	– 08	05	15	– 04	15	– 15	.33	15	.09	.23
Duration	26	10	30	.05	07	–.07	– 05	– 18	29	17	13	19	11	.53	07
Degree f control	01	07	13	20	.57	19	05	22	– 12	05	16	.24	– 03	.02	–.06
N f hospitalizations	14	10	33	16	.38	.07	48	.54	41	42	43	41	10	.30	–.05
Hypoglycemic onvulsions	02	08	31	24	.38	.07	.01	02	.01	.27	19	.36	.20	– 16	66
Head njury	.28	30	14	23	28	–.08	– 12	14	–.09	–.03	–.04	.02	.05	.07	– 12
Abnormal d livery	10	.01	02	01	10	–.09	14	11	– 19	– 15	– 31	.08	– 02	– 03	– 09
Birth weight	38	36	43	11	10	13	– 01	.21	.24	– 25	03	–.53	10	17	–.01
Neonat l complications	.05	01	13	11	44	03	– 16	– 27	15	– 12	– 27	– 09	.06	.03	12
Pertussis	10	10	18	42	47	37	– 01	–.23	13	– 13	– 23	–.09	– 08	09	–.20

$p < 0.05$

T total material (n 55)
Db = boys (n 27)
Dg girls (n 28)

		n=55	n 27	n=28
Confidence level	01	.36	.53	.52
	05	.27	40	.39

VI SUMMARY

The personality development in 59 diabetic schoolchildren 27 boys and 32 girls, aged 7–15 years has been studied. The duration of the disease exceeded one year varying between 1.1 to 13.2 years.

The assessment comprised an intelligence test, a series of projective techniques, interviews with the children their parents and teachers, and an EEG investigation. The results of the personality assessment have been correlated to clinical data about the disease to the attitudes of the parents and to the EEG findings.

In the assessment of the personality structure emphasis has been put on basic developmental concepts such as body image, ego structure and identification processes, on cerebrolesional traits and perceptual disturbances, and on emotional deviations.

The development of the body image and the identification processes are disturbed in the majority of the children, but ego weakness occurs only in few children largely indicating efficient defense mechanisms. These disturbances of fundamental processes are correlated to the attitudes of the parents towards the child and his disease The mothers mostly carry the burden of the daily management of the diabetic child and often find it difficult to cope with the disease

Cerebrolesional traits and perceptual disturbances are also common in the diabetic children. These deviations correlate to the occurrence of hypoglycemic convulsions and to different EEG abnormalities such as low alpha frequency paroxysmal activity and lack of diffuse responses at hyperventilation.

The EEG patterns of diabetic children differ significantly from those of healthy children in many respects. Unequivocally abnormal EEG records were found in 5 of the diabetic children.

Neurotic signs in the tests as well as clinical symptoms such as school problems, peer problems, vegetative symptoms and signs of anxiety and aggression occur in many diabetic children They are part of the child's direct reaction to his life-situation but they ar also related to disturbances of the basic processes (development of body image ego structure and identification) and to cerebrolesional and perceptual disturbances.

Table 29 Correlations between electroencephalographic patterns and relevant clinical data

	Alpha frequency			Alpha amplitude			Diffuse response to hyperventilation			Total paroxysmal activity			14 – 6 – PS		
	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg	T	Db	Dg
Age at onset	23	27	17	12	31	08	05	15	– 04	15	– 15	.33	15	.09	23
Duration	26	10	30	.05	07	–.07	– 05	– 18	29	17	13	19	11	.53	07
Degree of control	01	.07	13	.20	–.57	19	05	22	– 12	05	16	.24	– 03	.02	–.06
No. of hospitalizations	14	10	33	16	.38	07	48	.54	41	42	43	41	10	.30	–.05
Hypoglycemic convulsions	02	.08	31	24	.38	07	01	02	.01	27	19	.36	.20	– 16	.66
Head injury	28	30	14	.23	.28	–.08	– 12	– 14	–.09	–.03	–.04	.02	.05	.07	– 12
Abnormal delivery	10	01	02	01	10	– 09	– 14	– 11	– 19	– 15	–.31	08	– 02	– 03	– 09
Birth weight	38	.36	43	11	10	– 13	–.01	21	.24	–.25	– 03	–.53	10	17	–.01
Neonatal complications	08	01	13	11	44	– 03	– 16	–.27	– 15	– 12	– 27	– 09	.06	.03	12
Pertussis	10	10	16	42	47	37	– 01	–.23	13	– 13	–.23	–.09	–.08	.09	–.20

$p < 0.05$

T total material (n 55)
Db = boys (27)
Dg girls (n 28)

	n=55	n 27	n=28
Confidence level .01	.34	.53	.52
.05	.27	40	.39

VIII REFERENCES

1. Abramowicz, L., Margolis, A. & Wawrzyniakiewicz, T. Electroencephalographic changes in the diabetic children. *Ped. Pol.*, 1969 *446*, 693–699
2. Ames, L., Metraux, R. & Walker, R. N., *Child Rorschach Responses.* New York: Paul B. Hoebe, Harper & Brothers, 1952.
3. Ames, L., Metraux, R. & Walker, R. N. *Adolescent Rorschach Responses.* New York. Paul B. Hoebe, Harper & Brothers, 1959
4. Bain, H. W. & Chute, A. L. Diabetes in schoolchildren. *Pediatric Clinics of North America*, 1965 *12*, 919–940
5. Bakvin, H. & Bakvin, R., *Clinical Managements of Behavior Disorders in Children.* Philadelphia, London, W. B. Saunders Company 1960.
6. Barker, L. & Barcal, A. Psychosomatic aspects of diabetes mellitus. In O. W. Hill (Ed.) *Psychosomatic Medicine –2.* London, Butterworths, 1970
7. Barnett, D. M., Emotional factors in diabetes. In Joslin, E. and Root, H. (Eds.) *Diabetes Mellitus* Philadelphia: Lea & Febinger, 1971.
8. Bender, L. *Instructions for use of the Visual Motor Gestalt Test.* New York. American Orthopsychiatric Association, 1946
9. Bender, L. *Psychopathology of children with organic brain disorders.* Springfield Ill., C.C.T. Thomas, 1956
10. Benedek, T. A approach to the study of the diabetic. *Psychosomatic Medicine*, 1948, *10*, 284–287
11. Blaesing, S. & Brockhaus, J. The Development of Body Image in The Child. *Nursing Clinics of North America*, 1972, *7*, 597–607
12. Bernler, G. & Egg-Olofsson, O. In preparation.
13. Blum, G. S. *The Blacky Pictures. A Technique for the exploration of personality dynamics.* New York. Psychological corporation, 1950
14. Bohm, E. *Lehrbuch der Rorschach Psykodiagnostik.* Bern. Hans Huber 1957
15. Brandt, L., Nordén, A., Schersten, B. & Tryding, N. A diabetes detection campaign in southern Sweden. *Acta Medica Scandinavica*, 1964 *176*, 1955
16. Bruch, H. Physiologic and psychologic interrelationships in diabetes in children. *Psychosomatic Medicine* 1949 *XI* 200–210
17. Byrd, ... he Clinical ... bility of the Bender Gestalt Test with Children. A developmental Comparison of Children in Need for Psychotherapy and ren judged well adjusted. In. B. J. Marstein (Ed.) *Handbook of projective techniques.* London. Base Books, 1968.
18. Cerasi, E. & Luft, E. What is inherited and what is added. Hypothesis for the pathogenesis of Diabetes Mellitus. *Diabetes*, 1967 *16* 615
19. Child, D., *The Essentials of Factor Analysis.* London, New York, Sydney, Toronto. Holt, Rinehart & Winston, 1970
20. Dawson, M. E. & Greville, G.D. Biochemistry. In J. D. N. Hill and G. Parr (Ed.) *Electroencephalography.* 2 nd ed. London. McDonald, 1963
21. Dunbar, F. Wolfe, T. P. & Rioch, J. McK., Psychiatric aspects of medical problems. *American Journal of Psychiatry.* 1936, *93*. 649
22. Egg-Olofsson, O. & Petersén, L. Childhood Diabetic Neuropathy. A Clinical and Neurophysiological study. *Acta Paediatrica Scandinavica.* 1966 *55*, 163–176.
23. Egg-Olofsson, O. The development of the electroencephalogram in normal children and adolescents from the age of 1 through 21 years. *Acta Paediatrica Scandinavica*, 1970, suppl. 208.
24. Egg-Olofsson, O. The development of the electroencephalogram in normal children from the age 1 through 15 years. 14 and 6 Hz positive spikes phenomenon. *Neuropädiatrie*, 1971 *4* 405–427
25. Egg-Olofsson, O., Petersén, I., & Selldén, U. The development of the electroencephalogram in normal children from the age of 1 through 15 years. *Neuropädiatrie* 1971 *4* 375–404
26. Egg-Olofsson, O. & Petersén, I. In preparation.
27. Erikson, E. H., The problem of ego identity *Journal of American Psychoanalytic Association*, 1956 *4* (1), 56–121
28. Erikson, E. H. The psychosocial development of children. In J. M. Tanner & B. Inhelder (Ed.) *Discussions on Child Development.* London. Tavistock Publications, 1963 ( ), 160–215
29. Erikson, E. H. The Syndrome of Identity Diffusion in Adolescents and Young Adult. In J. M. Tanner & B. Inhelder (Ed.) *Discussions on Child Development.* London. Tavistock Publications, 1963 (b), 133–168
30. Eron, L. D. Character – Projective. In Buros, O. K. (Ed.) *The Sixth Mental Measurements Yearbook*, Highland Park, New Jersey. The Gryphon Press, 1965 495–501.
31. Etzwiler, D. D. & Sines, L. K., Juvenile D

and it M magement, Family Social and Academic Implications. *Journal of American Medical Association* 1962 *181* 304

32. Lysold R. Cerebrale Storungen bei Diabetes mellitus und *electroencephalographische* Untersuchungen bei diabetischen Kindern. *M Kinderheilkunde*, 1966, *114* 94

33 Fenichel, O. *The psychoanalytic theory of neurosis*. London. Routledge & Kegan Paul, 1955

34 Fischer A. E. Factors responsible for Emotional disturbances in Diabetic children. *Nervous Child* 1948 *7* 78–83

35 Fisher S & Cleveland, S. L. *Body Image and personality* Princeton, New Jersey D van Nostrand Company 1958

36 Fisher S. A further appraisal of the body boundary concept. *Journal of Consulting Psychology* 1963 *27* 62–74

37 Fisher S & Fisher R. L. Body boundaries and patterns f body perceptions. Journal of Abnormal and Social Psychology 1964 *68* 255–262

38 Fisher S Body sensation and perception of projective stimuli. *Journal of Consulting Psychology* 1965 *29* 135–138

39 Fisher S. & Renik, O. D Induction of Body Image Boundary Changes. *Journal of Projective Techniques & Personality Assessment* 1966, *30* 429–434

40 Fisher S. *Body Consciousness. You are what you feel*. New York. Prentice – Hall, 1973

41 Freud, S *Formulations Regarding the two Principles in Mental Functioning. Collected papers* London Institute f Psychoanalysis nd Hogarth Press, 1924

42 Frey T & Forssman, H. Om elektroencephalogram hos pojkar med uppforandersubbningar. *Nordisk tidskrift for kriminalvidenskab* 1951 *39*·1 1 9

43 Frohman L A. Central nervous system. Control of carbohyd te metabolism. In Fajans, S S. & Sussman, K E (Eds) *Diabetes mellitus. Diagnosis and treatment* American Diabetes Association, Inc 1971 Vol III

44 Gamstorp, I. Conduction velocity of peripheral motor nerves in mental retard tion diabetes and various neu ological diseases in childhood. *Acta Paediatrica Scandinavica*, 1964 *53* 408

45 Gibbs F A & Gibbs, E. L *Atlas of electroencephalograph Vol III* Cambridge Addison-Wesley Publ C Inc 1964

46 Greenberg, I M *Clinical Correlates of fourteen and si cycles per second positi electroencephalographic spikes and famil pathology* Doctoral thesis in the depa tment of psychiatry Downstate Medical Center B ookly New York 1968.

47 Gunther O Cereb ale Dauerschaden bei Diabetikern nach Hypoglykamie *Zeitschrift fur klinische Medizin*, 1958 *155* 125 157

48. Hagne L. Development f the EEG in normal infants during the first year of lif A longitudinal study *Acta paediatrica scandinavica*, 1972 supplement 232

49 Helk M., Schadisch, M. & W ink H. Das Electroencephalogramm des diabetischen Kindes. *Z. ges. Med.* 1962, *17* 616

50. Holley J W Fobarj, G & Ekberg, k On validity of the Rorschach test. *Scandinavian Journal of Psychology* 1965 *6* 7–18

51 Holley J W & Guilford, J P A N te on the G-index of Agreement. *Educational Psychological Measurement* 1964 *4* 749–753

52. Holley J W *Studies related to Q-R factoring* Doctorial dissertation, University of Gothenburg, 1966

53 Holley J W The Methodology f Rorschach Validation. *International Congress of Rorschach & Other Projects Tech iques*, 1971 *7* 682 689

54 Hughes, J R., Gianturco, D & Stein, W Electro-clinical correlations in the positive spik phenomenon. *Electroencephalography and Clinical Neurophysiology* 1961 *13* 599 605

55 Hutt, M L *The Hutt Adaptation of the Bender Gestalt Test* New York Grune & St tton, sec Ed 1969

56. Inagaki, T Miki, E., Maruyama, H & Sugiura, S., Electroencephalographic findings in childhood diabetes. *Brain Development*, (Jap) 1971 *3* supp.

57 Israel, J *Socialpsykologi*. Stockholm Svenska bokforlaget, 1963

58 Jacob son, T Huhmar E & Ramön, R Electroencephalographic alter tions in Diabetes Mell tus. *Acta Medica Scandinavica* 1966 *180* 441–448.

59 Jochmus, I Die psychische Ent icklung diabetischer Kinder und Jugendliche *Arkiv fur Kinderheilkunde*, 1971 *66*, Beiheft

60. Johnsson, G & Kaiverstein A-L., *2 2 Stockholmspojkar* Stockholm Almq ist & Wiksell 1964

61 Karon B P Problems f Validities. In A. I Rabin (Ed.) *Projective Techniques in Personality Assessment*. New York Springer Publishing Company 1968

62 Kaufman, R V & Hersher B Body Image Changes in Teen-Age Diabetes. *Pediatrics*, 1971 *48* 123 128

63 Kellaway P Crawley J W & J Kagawa, N A specific electroencephalographic correlate of convulsive equivalent disorders in children. *Journal of Pediatrics*, 1959 *55* 58 –592.

64 Kellaw y P C awley J W & Kagaw N Paroxysmal pain and tonomic disturbances of cerebral origin. A specific electro-clinical syndrome *Epilepsia*, 1960 *1* 466 483.

65 Kennedy W B Psychologic problems of the young diabetic *Diabetes*, 1955 *4* 207 209

66 Klopfer B & Davidson, H H *The Rorschach Technique* A I troductory Manual New Y rk Harcourt, 1962

67 Koski, M-L. The coping process in childhood diabetics. *Acta Paediatrica Scandinavica*, 1969 Suppl 198

68 Kubany A. J. Danowski, T. S. & Moses, C. The Personality and Intelligence of Diabetics. *Diabetes*, 1956 5 462–467

69 Larsson, Y & Sterky G. Long-Term Prognosis in Juvenile Diabetes Mellitus *Acta Paediatrica*, 1962, Suppl. 130

70. Lemere F The significance of individual differences in the Berger rhythm. *Brain*, 1936 59 366 375

71 Leonardt, I Das diabetische Kind in der elterlichen Konfliktsituation. *Psychotherapie*, 1957 2, 206–218.

72 Levitt, L., Lubin, B & Zuckerman, M. A simplified Method of scoring Rorschach content for dependency *Journal of Projective Techniques*, 1962, 26 234–236.

73 Lipowski, Z. Y Physical illness, the individual and the coping process *Psychology in Medicine* 1970 2, 91–102

74 McGavin A. P Schultz, L., Peden, G. W & Bowen, B D., The Physical Growth, the Degree of Intelligence and the Personality Adjustment of a Group of Diabetic Children. *New England Journal of Medicine*, 1940 223 119–127

75 Mead H G., *The social psychology of George Aubert Mead*. Chicago Anselm Strauss, 1956.

76 Meissner A., Thoreson, R. & Butler A The impact of obvious physical handicap on male and female self-concept. *Perceptual and Motor Skills*, 1967 24 1099–1105

77 Melchior J C The Incidence of Head Injuries in Children. *Acta Paediatrica*, 1961 50, 47–50.

78 Nursing Times Editorial How thalidomide children see themselves. *Nursing Times*, 1969 April, 24 519–522

79 Niedermeyer, E. & Knott, J R *Über die Bedeutung der 14 und 6/sec-positiven Spitzen im EEG Archiv für Psychiatrie und Nervenkrankheiten* 1961 202, 266 280

80 Pacella, M Inter-Examiner on the Bender Gestalt test. *Journal of Clinical Psychology* 1962, 6, 18 23

81 Pankow G. Familienstruktur und Psychose. *Psychotherapy and Psychosomatics*, 1968 16 366 374

82 Pascal, G. & Suttell, B *The Bender Gestalt Test*. New York Grune & Stratton, 1951

83 Paul, J & Schmitzer E Soziale Anpassungsschwierigkeiten bei diabetischen Kindern und Jugendlichen *Medizinische Klinik*, 1966 61 789 794

84 Petersen I & Eeg-Olofsson, O The development of the electroencephalogram in normal children from the age of 1 through 15 years. Nonparoxysmal activity *Neuropädiatrie* 1971 2, 247

85 Piaget, J & Inhelder B *The growth of logical thinking from childhood to adolescence* New York Basic Books, 1958

86. Reske-Nielsen, E., Lundbæk K. and Rafaelsen, O J Pathological Changes in the Central and Peripheral Nervous System of Young Long-term Diabetics *Diabetologia I* 1965 233–241

87 Robins, L. N., *Deviant children grown up*. A sociological and psychiatric study of sociopathic personality Baltimore Williams and Wilkins, 1966

88. Roll, L. & Alpert, R. *Identification and child rearing*. Stanford Cal. Stanford University Press, 1965

89 Rorschach H., *Psychodiagnostik*. Methodik und Ergebnisse eines wahrnehmungsdiagnostischen Experiments. Bern Hans Huber 1941

90 Sappenfield. B. R., Character – Projective. In O. K. Buros (Ed.) *The Sixth Mental Measurement Yearbook*. Highland Park New Jersey The Gryphon Press, 1965 417–423.

91 Sears, R. R. Personality and motivation *Review of Educational Research* 1944 14(5), 368–371

92. Sears, R. R.. Social behavior and personality development. In T Parsons & E. A. Shils (Ed.) *Toward a general theory of action*. Cambridge, Mass., Harvard University Press, 1951

93. Selstam, U Karlberg, P & Landstrom, I *Experiences with modifications of medical birthrecords*. Paper presented at the meeting of the Swedish Paediatric Society in Goteborg, April 21 1971

94. Sheppe, W M. & Sheppe W M. Jr The Psychogenic Problems of the Young Diabetic Patient. *West Virginia Medical Journal*, 1954 50 65–69

95 Starr P H Psychosomatic Considerations of Diabetes in Childhood. *Journal of Nervous and Mental Disease*, 1955 121:6, 493 504

96 Steigerwaldt, F Das diabetische Schulkind. *Medizinische Klinik*, 1963 13 524

97 Sterky G. Diabetic Schoolchildren. *Acta Paediatrica Scandinavica*, 1963 a, Suppl. 144

98. Sterky G., Family background and state of Mental Health in a group of Diabetic Schoolchildren *Acta Paediatrica Scandinavica*, 1963 b 52, 377 390

99 Stevens, J R., Sachdev K. & Milstein, V Behavior disorders of childhood and the Electroencephalogram. *Archives of Neurology* 1968 18, 160 177

100. Strauss, H Clinical and electroencephalographic studies. The electroencephalogram in psychoneurotics *Journal of Nervous and Mental disease*, 1945 101 19–27

101 Swift, C. R., Seidman, F & Stein, H Adjustment Problems in Juvenile Diabetes *Psychosomatic Medicine* 1967 29 555–571

102. Sodering, B Behandlung der Zuckerkrankheit im Kinderalter ohne Diätbeschränkungen *Acta Paediatrica*, 1935 Suppl. 2.

103. Travis, A. S. *Management of Juvenile Diabetes Mellitus*. New York. C. V. Mosby Company 19 1

104 Treuting, T F The role of emotional factors in the etiology and course of Diabetes Mellitus A review of the recent literature *American Journal of Medicine sciences*, 1962 131 244

105 Tieffry J C & Mallet, A Complications

diabete infantile. *Archives françaises de Pédiatrie* 1972 *29* 957–964

106 Ulett, G. A., Gleser G Winokur G & Lawler A The EEG and reactions t photic stimulation as n inde of anxiety-proness. *Electroencephalography and Clinical Neurophysiology* 1953 *5* 23–32.

107 Wadenbergh, R. L., Sassman, K. L. & Trims, C C Effects of Hypnotically Induced Acute Emotional Stress on Carbohydrate and Lipid M tabolism in Patients with Diabetes Mellitus. *Psychosomatic Medicine* 1966 *28*, 382.

108. Walter G., Electroencephalographic Development of Children. In J M Tanner & B Inhelder (Eds.) *Discussions on Child Development* London: Tavistock Publ. 1956, 132–160.

109 Walte R. D., Colbert, E. G., Hoegler R. R Palmer, J O. & Bend P M A Controlled study of the fourteen and six per second EEG pattern *Archives of General Psychiatry* 1960 *2* 559–566

110. White P., *Diabetes in Childhood and Adolescence.* New York Lea & Febiger 1932

111 White P & Graham, Ch. A The Child with Diabetes. In E. Joslin & H Root (Eds.) *Diabetes Mellitus*, Philadelphia Lea & Febiger 1971

112. Williams, J J Disease as deviance. *Social Science and Medicine* 1971 *5* 219–226

113 Wolff S. & Olatawura, M., *Psychiatric disorders of diabetic children and their mothers.* Congress Paper London, 1971

114 Wortis, J *Recent Advances in Biological Psychiatry* New York Plenum Press, 1963

115 Zeidel A. Emotional adju tment of juvenile diabetics and thei families. In Zvi Laron (Ed.) *H bilitation and rehabilitation of juvenile diabetics* Leiden. H E. Stenfert K ose N. Y 1970, 159–166

116 Zierl, W Zu seelischen Entwicklung des diabetischen Kindes. *Ärzte Wschr* 1954 *41* 974 981

IX APPENDICES

Appendix I

Questions in the interviews. Scoring of answers

Parents

1 How did you react when you was informed that your child has diabetes?
Reaction scored as composed =1 despair =2 shock =3

2 How have you been able to cope with your child s disease?
Degree of adaptation scored as easily adapted =1 adapted with difficulty =2 not adapted =3

3. Do you find difficulties in following the dietary prescriptions?
Answer no =1 yes =2.

4 Who gives the insulin injections?
Do you find it disagreeable to give your child injections?
Answer no =1 earlier but not now =2, yes =3

5 Do you think that the disease will influence your son s (daughter s) choice of profession?
Answer no =1 yes =2.

6. What do you think about the information you have g t on the diabetic disease?
Answer good =1 fair =2 bad =3

7 Who takes the responsibility when problems appear concerning the diabetes, you or your wif (husband)?

8 Do you find it difficult to be conseq ent in the rearing of your child?
Answe "yes" or we do not try to be consequent scored 1 "no" scored 2.

9 Do you give special instructions when he (she) is going out? Which?
0–2 scored 1 more than 2 scored 2.

10 Do you think one ought to protect on s child from unpleasant experiences as much as possible
Answer no =1 yes =2.

11 Do you think that you child should realize his (her) possibilities and limitations as early as possible?
Answer yes =1 no =

12. At what age do you think that your child can be away from home for several days (e.g. can be sent t a scout camp)?
Answer "at 10–12 years of age" =1 "after 12 years of age" =2.

13 Do you prefer that your child spends his (her) spare time at home?
Answer no =1 yes =2.

14 Are you a member of the association for parents of diabetic children?
Answer yes =1 no =2.

15 Do you regularly go to the cinema (to the theatre, to football matches etc.) with your child?
Answer yes =1 no =2.

16 Do you regularly take physical exercise with your child?
Answer yes =1 no =2.

17 Has your child any school problems?
Answer no =1 yes =2.

18. Has your child problems with his (her) peers?
Answer no =1 yes =2.

19 How often does your child lose his (her) temper?
Answer never" or "seldom" =1 " t least once a week" =2

20. How does the child behave when he (she) loses his (her) temper?
Answers indicating that the child gives obvious expression to his (her) anger scored 1 answers indicating suppression of the anger (e.g. "he walks into his room") scored 2.

21 How does your child behave when you have guests?
Answers indicating shyness or anxiety scored 2.

22 How does your child react to the visits to the doctor?
Answers indicating anxiety scored 2

23 How has your child reacted to the hospital admissions?
Answers indicating anxiety scored 2

Appendix I 2

Teachers

1 Do you know that has diabetes mellitus?
Answer yes =1 no =2.
2. When and how did you get that information?
3 Does his (her) classmates know that he (she) has diabetes?
Answer yes =1 no =2
4 Has the child any school problems?
Answer no =1 yes =2.
5 Has the child any problems with his (her) classmates?
Answer no =1 yes =2.
6 Do you know if the child has any problems in the school refectory?
Answer no =1 yes =2.
7 Are your contacts with the parents satisfac tory?
Answer yes = 1 no = 2

Appendix I 3

Children

1 What do you like to do when you get home from school?
2 Which are your hobbies?
3 Do you regularly take physical exercise after school?
Answer yes =1 no =2.
4 Have you any problems with your peers?
Answer no =1 yes =2
5 If you could wish three things, what would they be?
No expressed wish about the disease =1 a wish for health =2
6 What did you think when you were told that you had got diabetes?
7 Which profession would you chose when you are grown up?
8. What is your greatest problem now?
Answers indicating worry for the future scored 2
9 Have you told your schoolmates that you have diabetes?
Answer yes =1 no =2.

supported by the correlation between "orig–" answers and the low alpha frequency and the correlation between F(C) answers, which are produced by the perceptually advanced and high alpha frequency (Table 27)

The association between the 14-6-PS phenomenon and behavior variants has been studied extensively. The incidence of this EEG pattern in psychiatric disorders has been investigated by among others, Walter et. al. (109), Niedermayer & Knott (79), Hughes et. al. (54) and Greenberg (46). Walter et. al. (109) found a relation between 14-6-PS and aggressive behavior emotional disturbances and disturbed family relations. In a study of adolescents with psychiatric disorders Bernler & Eeg-Olofsson (12) obtained significant correlations between this EEG pattern and aggressivity and anxiety. The present study shows that these correlations also exist in a younger age group (Table 26). The correlation between 14-6-PS and neurotic traits is further emphasized by the correlations between that EEG pattern and "cloth" answers and "mirror interpretations" (Table 27).

Paroxysmal activity has usually been regarded as a definitely abnormal pattern. However it occurs in seemingly healthy children, and can be provoked by different stimuli. Probably its clinical significance depends on its way of appearing; *spontaneously during sleep or provoked by photic* stimulation. In the diabetic boys paroxysmal activity mainly appeared at rest or during sleep was correlated to perceptual disturbances and to paroxysmal symptoms and thus can be regarded as a pathologic pattern.

In summary: The deviations of EEG patterns in diabetic schoolchildren are correlated mainly to perceptual difficulties, cerebrolesional traits and emotional disturbances, but very few correlations to items concerning body image development, ego structure and the identification process are obtained. The lesional-perceptual disturbances do not then seem to be severe enough to influence the basic developmental processes.

Irrespective of the interpretation of the obtained correlations between EEG patterns and test items, these correlations are of interest. Firstly they give new possibilities to evaluate the nature of the EEG patterns, secondly they reinforce the validation of the psychological assessments. The correlations between EEG patterns and clinical somatic data (Table 29) indicate that both the diabetic metabolic disturbances and factors not connected with the diabetic disease as low birth weight and previous head injury may be responsible for the EEG deviations found in the diabetic group.

R factor analysis

The items included in the R-factor analysis and the rotated factor matrix are given in Appendices VIII and IX. Oblique rotation for simple loadings was used. The analysis gives 13 factors explaining 80 per cent of the variance The final communalities are high (65–95) and the intercorrelations bet ween the factors do not exceed 19 The factors are all first order factors.

Factor I

School problems	.91
Opinion of obtained information (mother)	.87
Barrier scores	.85
Social group	.85
Hospitalizations	75

This factor demonstrates the importance of the social background Low socio-economic status is associated with dissatisfaction concerning informa tion about the disease a high number of hospita lizations, tendencies to isolation and school difficulties.

Factor II

No activities together (mother)	.93
Penetration scores	93
Peer problems	40

Factor IV

No physical activity together with the child (mother)	.97
Ego weakness	.97
WISC	.59

Factor VI

Neurotic index	.90
Reaction to first information (mother)	77
Anxiety index	.59
Coping with the disease (mother)	.57

Factor XII

Object criticism	77
Prefers to have the child at home (mother)	.55
Cerebrolesional index	.51

These four factors illustrate the connection between the mother's attitudes and deviations in the child's personality structure Her reaction to the first information about the child's disease seems to influence the family's coping with the disease and an uncontrolled reaction is associated with anxious and neurotic traits in the child (Factor VI) Lack of interest in the child's activities seems to have an effect on the development of the body image and the ego structure (Factors II and IV) This may lead to peer problems (Factor II). According to Factor IV the gifted child is more affected by the lack of interest.

Factor V

Diffuse response to hyperventilation	–.85
Perceptual disturbance index	.68
Maladjustment index	.54

Factor IX

Polyphasic potentials	85
Alpha amplitude	79

Factor X

Alpha frequency	– 94
Maladjustment index	41
(Paroxysmal activity)	(.39)

Factor XIII

Paroxysmal activity	.67
Hypoglycemic convulsions	.60
Duration of disease	.54
Hospitalizations	41

These factors all contain EEG variables. Paroxysmal activity is related to hypoglycemic convulsions (Factor XIII). A long duration of the disease is of importance to establish this relationship Lack of diffuse response to hyperventilation is related to pahtological scores in the Bender test, i.e the perceptual and maladjustment indices (Factor V) In children with low alpha frequency paroxysmal activity is frequent and so is scoring on the maladjustment index (Factor X).

Factor III

Emotional lability	78
Identity index	75

Factor VII

Age at onset	.83
Age	.75
Degree of control	.41
Peer problems	–.44

Factor VIII

Paranoid traits	.79
Aggressivity	.76
(Peer problems)	(.39)

Factor XI

Tics, nailbiting, etc.	.81
Hypoglycemic convulsions	.67
Degree of control	.44

These four factors give interactions between psychological variables or between clinical and psychological variables. Factor III shows an association between identification problems and emotional lability. Paranoid and aggressive behavior are connected with peer problems (Factor VIII). Peer problems in young children can also be associated with early onset of the disease and good control (Factor VII). Factor XI shows that clinical signs of anxiety (tics, nailbiting etc.) occur in children with bad control and hypoglycemic convulsions.

The aim of the R-factor analysis was to find patterns of interaction between important items revealed by the correlation analyses. The R-analysis has given such patterns confirming and completing the intercorrelations between the personality traits and different background variables. Statistically the factors are on a general explanatory level.

V GENERAL DISCUSSION

The aim of the present investigation has been to give a comprehensive account of the personality structure in diabetic schoolchildren. To fulfil this purpose a battery of personality tests was used. In order to understand the individual personality patterns these should be related to the environment of the child and his reactions to the environmental conditions. The psychological assessments have therefore been correlated to clinical variables and to the attitudes of the environment. Since electroencephalographic abnormalities have been demonstrated in diabetic children (1, 22, 32, 49, 56, 59) an electroencephalographic examination was included as a correlate to the personality assessment.

Earlier investigations on the personality structure of children with diabetes have often been focused on isolated variables. When a broader assessment has been made, the intercorrelations between the different variables have not been considered in detail. One essential element of the present investigation has been the effort to get an understanding of these complex connections by means of different types of correlation analyses.

Material

The investigated group of diabetic schoolchildren is medically – therapeutically homogenous. The group comprises the majority of diabetic schoolchildren in an urban community in Sweden. The number of missing cases is comparatively small and the results can be regarded as representative of diabetic children through the ages 7–15 years living under these conditions.

In the present investigation a correlation between tion of the diabetic material concerning age and duration of the disease (Table 2) should be considered. Thus, the age group 12:6–15:5 years comprises 45 per cent of the material. There were few girls in the age group 6:6–9:5 years and few boys aged 9:6–12:5 years. The onset of the disease occurred before the age of 5 years in 53 per cent of the boys but only in 25 per cent of the girls.

The differences in personality structure between the two sexes found in the present study may partly depend on this skewness of the material. However, to a certain degree they can be an expression of a difference in the reactions between boys and girls. It is wellknown that girls reach emotional and social maturity earlier than boys. This maturity means a better understanding of the own life situation but also increased vulnerability. Thus, in the Rorschach test the diabetic girls gave more responses indicating mature personality as well as responses denoting emotional disturbances.

Concepts and methods

In the present investigation the personality structure has been described through projective techniques, supplemented by interviews. Projection can be regarded as a normal psychological phenomenon implying that a person's earlier experiences, feelings, needs and attitudes influence his perception of the surrounding world both in the direction of selection and interpretation. By means of projective tests information about different aspects of the personality structure are made available. The results have been presented in terms and concepts which are wellknown and have been discussed earlier. In this context only the maladjustment index will be commented upon. As mentioned earlier this index consists of five Bender items, which have been found to differentiate between "well adjusted" children and children with different emotional and behavioral disturbances but without obvious signs of cerebral lesion (17). In this study the maladjustment index and the perceptual disturbance index to a large extent correlate to the same background variables (Tables 16, 22 and 26) and show a high intercorrelation (.85). The two indices probably have a similar

basic structure but in the maladjustment index the perceptual difficulties have led to clinical symptoms (Table 18).

In this investigation many intercorrelations have been studied and the risk of obtaining significant correlations by chance must be taken into consideration. Isolated significant correlations should be interpreted with caution especially if one of the items includes few individuals. If significant correlations are distributed into interpretable patterns, they probably represent true relations between the variables. Significant intercorrelations do not prove but can suggest the existence of causal connections.

Results

The investigated diabetic children have an IQ above the average which is in agreement with earlier investigations (5 31 97 101 110). This finding has usually been attributed to an over representation of diabetic families from higher social groups, an explanation which cannot be valid in the present study of a representative group. The correlation between intelligence and early onset of the disease (Table 16) is of interest, but difficult to interpret.

The different psychological tests and the interviews consistently disclosed an increased frequency of basic developmental disturbances and adjustment problems among the diabetic children when compared to the controls. The disturbances concern fundamental developmental processes such as the development of body image and ego structure and the identification process. A high frequency of perceptual disturbances and deviations describable in psychopathologic terms such as neurotic traits, anxiety aggressivity and paranoic reactions were also found.

Disturbed body image development in the diabetic children is indicated by the frequencies of "barrier and penetration" scores on the Rorschach test (Table 4 Appendices VI and VII). A disturbed body image is a common feature in the diabetic group which agrees with earlier investigations demonstrating that in the presence of chronic disease or physical handicap a negative body image is a frequent finding (11 6 76).

The concept of body image is closely related to that of ego structure. The development of the body image is one of the bases for the formation of an ego. Bodily experiences during the first years of life are according to psychoanalytic theory important to the subsequent development of the ego (27). Later the social environment expands tremendously and during the years from school entrance to adolescence the interaction with peers and the crystallization of the sex role influence the ego development. During this period the child experiences either a sense of inferiority or of industry and develops different defense mechanisms in order to keep the ego structure intact. It is therefore interesting to notice that in spite of the common occurrence of body image disturbances, few diabetic children (7 out of 59) have a weak ego structure. This small number may of course depend on the criterion of ego weakness applied in the present investigation. However even with a broader definition of ego deficiency the number of diabetic children with weak ego structure would be comparatively small. It is because of this probable that most of the diabetic children during the progression of their disease have developed effecient ego defense mechanisms, e.g. different neurotic reactions such as aggressivity or critical attitudes.

Many diabetic children have obvious difficulties with their identification. This is evident from the content of the "strong" spontaneous stories on the Blacky Pictures (Tables 6 and 7) and from the content of the factors of that test. To a large extent these deal with poor relating and communicating within the family unit, i.e. feelings of parental deprivation and feelings of isolation. This means that the child lacks adequate identification prototypes. The content of fact 1(Db) of the Rorschach test deals with social difficulties, isolation and stagnation which also indicates identification problems.

The finding of identification difficulties among children with a high frequency of body image disturbances is not surprising. Nevertheless, the high frequency of themata in the Blacky Pictures test indicating poor family relations should be paid attention to since the diabetic child is dependent on his family in coping with his disease. One consideration is that the family is too occupied by the daily routine necessary for the management the disease to be able to establish normal e nal elations. This line of thought gets

from the correlations between disturbances in the child's body image ego structure and identification and the attitudes and reactions of the parents towards the disease and its implications (Tables 22 and 23). There are also associations between these disturbances and the parents degree of interest in the child's activities and the parental attitudes of overprotection The relations between the attitudes of the family and fundamental developmental processes are stressed by the results of the R-factor analysis. Children with disturbed body image ego structure and identification problems have school problems, peer problems and manifest aggressive and anxious behavior (Table 18, R factor analysis) In contrast significant correlations to clinical somatic data and to EEG phenomena are comparatively few (Tables 17 and 26)

In previous psychological assessments of diabetic children little attention has been paid to the occurrence of cerebrolesional traits. In the present investigation the Bender Visual Motor Gestalt test revealed significantly more signs of perceptual disturbances in the diabetic group than in the controls (Tables 9 and 10). Several of these signs are often found in organic cerebral diseases. The presence of cerebral dysfunction in the diabetic children is further supported by frequent scoring on the cerebrolesional index (Appendices VI and VII) and by the deviating EEG patterns (Table 24)

In the diabetic girls cerebrolesional traits and perceptual disturbances (Table 16) as well as paroxysmal activity on EEG (Table 29) are correlated to hypoglycemic convulsions. A relation between hypoglycemic attacks and permanent encephalopathy and/or EEG abnormalities has been found in diabetic children by several authors (1 32, 47 49 59) who regard the hypoglycemia as a cause of diabetic encephalopathy Other metabolic defects of the diabetic disease should also be considered in this context. Some authors have suggested the existence of a primary diabetic encephalopathy with hypoglycemic episodes as a secondary manifestation (58 86)

In the present investigation a correlation between perceptual disturbances and head injuries is found in the diabetic boys (Table 17) Head injuries as well as other peri- and postnatal events can be contributory factors in the genesis of perceptual disturbances. The incidence of such events in the diabetic group (Table 3) is, however about the same as that reported in unselected groups of children (77 93) and can not explain the high frequency of perceptual disturbances in the diabetic group

The deviating EEG patterns found in the diabetic group are essentially of the same kind that have been reported earlier by Eeg-Olofsson and Petersén (22) In the present investigation the EEG records of the diabetic children have been analysed related to the development of the EEG in normal children and adolescents recently described (23) In comparison with previous reports (1 32, 49 59) comparatively few EEG records have therefore been classified as definitely abnormal. The correlations to the personality structure mainly concern cerebrolesional traits and perceptual disturbances (Table 26). There are also significant correlations to emotional disturbances, while associations to basic developmental processes are rare

Although only three of the diabetic children (two boys and one girl) had been in contact with a child psychiatrist projective techniques and inter views disclose a high frequency of emotional disturbances and behavior deviations in the group. Neurotic symptoms are common in the form of aggressive behavior anxiety paranoic traits and emotional lability (Appendices VI and VII). School problems and peer problems also occur more frequently in the diabetic children than in the controls. The two sexes display the same types of reactions, but on the whole the girls are more prone to neurotic manifestations than the boys.

The pattern of the intercorrelations and the result of the R-factor analysis indicate that the emotional disturbances and the behavior problems are related both to cerebral dysfunction and to deviations in the development of body image ego structure and the identification processes.

It has been stated (7 43 102 104) that emotional disturbances influence the course and the control of the diabetic disease in a negative direction by the imposed stress. In this investigation emotional disturbances have not been found to correlate with the degree of control but they are related to hypoglycemic convulsions.

Intelligence above the average level, body image disturbances, identification problems, perceptual difficulties and neurotic symptoms are typical findings in the diabetic child. The factor analyses

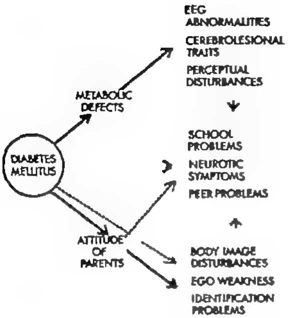

Fig. 4 Possible mechanisms for the personality deviations in children with diabetes mellitus.

do not, however establish the existence of a specific diabetic personality. Thus, the demonstrated deviations do not manifest themselves in a uniform pattern, but the various basic personality structures still play an important role.

In about one third of the diabetic children the disturbances can be characterized as profound (obvious neurotic symptoms, evident perceptual disturbances and/or ego weakness). This figure can be compared with those given by Swift et. al. (101) Jochmus (59) and Koski (67) all reporting a frequency of approximately fifty per cent of significant deviations. The prognostic significance of the demonstrated deviations cannot be evaluated without a follow up of the investigated group. Zeidel (115) states that after increasing difficulties during the adolescence adjustment is often achieved as the diabetic patients have learned to accept the reality and are able to cope with the disease. However Zeidel found a large group of young adults still in need of psychotherapy.

The results of the present investigation can be summarized in a tentative model, containing possible mechanisms for the disturbances found in the diabetic children (Fig. 4). In diabetes mellitus the metabolic defect(s) may lead to permanent cerebral dysfunction with resulting cerebrolesional symptoms and EEG abnormalities. The basic developmental processes are influenced in negative direction by the reactions and attitudes of the environment (parents) but also directly by the disease. Different neurotic symptoms and behavior deviations can be secondary to these disturbances. Thus, the high frequency of school problems in spite of a more than average intelligence most likely depends on the perceptual disturbances. Signs of maladjustment may also be a direct reaction to the disease or to the parental attitudes.

In the management of the diabetic child it is important to observe and evaluate the reactions and attitudes of many parents from the onset of the disease. Proper information may modify the first shock like reaction of the parents and the further attitudes towards the disease. This can be expected to have positive effect on the personality development of the child. Poor relations between the family members should be paid attention to because of their negative influence on the identifi-

cation processes. The parents should be encouraged to participate in the child's activities but overprotecting attitudes should be avoided.

The occurrence of perceptual difficulties needs to be evaluated and considered in the education of the child. Reading and writing difficulties should be searched for when the child reaches school age. In the treatment of the diabetic child one should be observent on hypoglycemic symptoms because of the association between hypoglycemia and perceptual disturbances. However further investigations are necessary to establish if the perceptual disturbances in diabetic children are an effect of the hypoglycemic episodes, or if both these manifestations depend on a basic cerebral lesion – a diabetic encephalopathy. Another interesting aspect on the relation between personality structure and diabetic disease needing further research is the influence of the premorbid personality on the course of the disease and on the individual's coping with it.

Appendix II

Q-factor analysis Rorschach. Rotated factor matrix. Db 1–27 Cb 28–54

Case	Factor 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	.26	–.26	–.05	.61	.21	11	.09	14	09	–.02	.38	.03	–13	–.03	11	.01
2	12	–.26	11	.27	40	12	26	.09	.07	.23	.33	.39	.06	–.03	19	–.03
3	.24	–.08	–15	.30	[illegible]	.36	05	17	11	–10	36	13	11	–.46	16	–10
4	.27	–.28	14	19	10	.20	.01	.39	46	10	17	.09	.05	.00	01	.04
5	15	–[illegible]	–.07	.38	.01	17	–00	40	09	.22	25	.28	–.28	–06	–09	19
6	14	12	.37	16	17	.22	–.08	.26	11	–.05	.33	10	–10	11	–.23	40
7	.30	–18	.03	15	14	05	–.02	.20	14	.03	74	–16	.01	–.01	09	12
8	.03	–10	[illegible]	.03	03	.01	–13	10	.09	11	–03	79	–13	–13	11	.05
9	.76	–17	09	.07	17	.04	.04	.02	.02	13	.27	–10	.04	–07	.03	17
10	.05	–.03	46	–.08	–.06	01	–18	01	–.01	11	02	.23	–11	–.67	12	.21
11	.09	.00	16	.01	16	05	–.05	–.04	.05	.02	.21	.06	–75	17	.06	.09
12	40	–79	.26	01	.09	.21	.26	.06	.33	.21	.22	08	–.21	–01	–19	–.03
13	–.01	–06	69	.05	–.03	.02	–17	17	06	.33	–.01	10	–19	–.05	.09	.07
14	–05	–13	–07	.30	11	.27	–00	33	.67	–06	.05	.01	–04	–10	.07	.09
15	–02	07	13	77	10	.02	13	04	24	.22	15	–02	.03	.08	–.05	13
16	.68	–12	–.06	.05	.24	08	–08	12	–.07	19	.26	.05	–13	.01	16	.07
17	10	–11	–.03	.02	.32	01	09	12	25	.24	–.05	–.04	–24	–.63	–00	15
18	.36	–.09	–.02	12	.23	–19	09	21	12	.03	57	01	–08	11	.21	13
19	15	–11	.03	.03	75	07	05	04	12	.05	13	–01	–10	–.05	12	11
20	–05	–.32	.26	.04	11	–.22	10	–06	58	.31	13	19	–12	–06	08	19
21	71	–.01	06	.01	.04	13	.26	03	16	.07	14	15	–06	–11	.03	.02
22	12	–05	.07	14	01	.21	–05	05	18	17	73	11	–06	–.09	11	14
23	16	–02	.03	13	03	.08	02	01	13	.02	15	.08	–09	17	.01	.83
24	18	13	15	02	.02	05	–.09	16	06	74	.05	11	–.23	–16	–.03	–.08
25	.09	–14	.09	.05	08	08	.00	77	16	07	18	12	[illegible]	–06	.06	.02
26	.34	–13	.52	.21	37	15	14	15	12	–00	02	–.06	.02	–.24	00	–13
27	.33	02	.09	03	61	11	17	11	17	–00	11	.09	–12	–.07	12	–.26
28	08	–.07	.05	04	.22	04	09	08	11	15	04	17	–12	–09	73	–04
29	05	.06	12	18	09	19	06	03	12	77	04	.01	16	–05	.24	.07
30	08	.35	11	.35	07	19	19	04	26	.04	–17	19	48	03	.24	08
31	.04	12	[illegible]	13	02	.62	25	09	03	16	33	–11	18	–.07	.35	15
32	.03	–15	02	.30	15	.59	00	26	10	.02	11	29	11	.03	07	.25
33	.24	20	14	09	04	04	71	[illegible]	00	14	09	11	–.08	14	10	–.03
34	.00	43	09	25	57	18	11	13	11	11	16	[illegible]	.05	.04	01	[illegible]
35	.03	[illegible]	15	04	29	19	41	[illegible]	17	17	46	[illegible]	–.30	05	10	.03
36	–.08	.09	[illegible]	29	23	20	08	25	.50	19	.27	.22	–10	–.26	15	.04
37	[illegible]	[illegible]	14	01	17	07	08	38	.62	04	21	03	04	14	.06	15
38	.20	.32	14	[illegible]	48	15	03	05	03	07	25	07	–06	–16	10	12
39	.39	–13	14	21	41	23	18	13	02	09	44	13	.23	–.06	03	05
40	31	30	11	.07	32	22	08	22	04	13	.53	.04	.22	11	04	–08
41	19	22	04	10	18	25	24	13	12	.34	.56	15	11	14	02	04
42	.36	[illegible]	05	23	10	49	09	16	39	.25	.02	07	09	.08	06	06
43	.39	35	02	09	34	47	07	01	28	17	09	13	–07	17	00	16
44	.21	36	03	06	21	44	.08	02	.23	14	16	–.07	31	06	15	01
45	18	45	04	06	08	24	06	06	.57	12	.23	12	–.05	02	08	06
46	[illegible]	19	05	0_	29	19	.01	09	42	–10	.24	.52	18	13	07	01
47	06	66	05	02	30	18	08	35	[illegible]	10	.09	–09	–12	09	13	11
48	07	59	05	19	6	25	24	13	22	.21	14	–04	06	09	14	05
49	08	26	20	14	27	14	30	11	48	.07	.02	–03	.31	04	17	01
50	10	48	13	03	24	15	19	08	18	.09	.36	.03	[illegible]	03	29	00
51	[illegible]	77	26	10	03	01	01	11	.04	–08	–.03	13	.01	01	[illegible]	01
52	16	20	03	10	26	66	03	10	06	14	[illegible]	.01	18	.20	[illegible]	.04
53	17	70	03	[illegible]	11	01	05	02	29	.09	.23	10	08	07	–02	
54	16	70	20	04	27	8	–16	.03	20	.07	15	.09	.04	02		

Appendix III

Q-factor analysis. R rschach. Rotated factor matrix. Dg 33–64 Cg 1–32

Case	Factor 1	2	3	4	5	6	7	8	9	10	11	12
1	.28	–07	.26	.24	.57	16	03	–11	18	21	.06	–11
2	.62	.06	.28	–11	6	–.22	16	09	04	09	–13	00
3	–13	71	01	–01	.03	–07	16	–07	08	07	02	–00
4	–.03	18	.04	–.06	.32	06	.54	–4	–17	–06	–14	–05
5	.69	.00	.02	.23	.08	44	–01	08	11	07	–18	–07
6	43	14	47	.09	19	.05	–11	00	14	01	–13	–46
7	.23	18	.20	45	41	.25	14	–09	01	17	–08	–05
8	16	.24	–03	43	.31	21	–01	–03	–05	15	–02	–.52
9	.63	01	18	.24	–00	10	06	.23	13	08	–.36	–06
10	73	–03	13	16	.23	.32	.08	–04	07	05	05	–02
11	.04	12	00	12	13	.04	–.02	.83	15	05	02	–03
12	.34	–09	.06	.59	.22	11	05	00	09	00	.02	–14
13	–10	.62	13	.03	.26	.25	–09	–16	.04	05	–00	–16
14	45	.06	17	.03	.68	08	–.00	–07	.05	08	–14	–09
15	74	–07	.22	17	04	15	05	–01	.21	–11	–02	–.22
16	16	.34	.08	14	.39	15	–.20	01	02	11	–07	–33
17	47	–11	13	.09	00	06	–04	–13	19	07	–09	–65
18	41	–.02	.51	.25	08	.30	–05	03	.23	02	–05	–27
19	.36	11	11	14	.23	43	.35	–14	–19	13	04	–12
20	.51	17	–12	14	18	–00	04	–02	03	.20	–.27	–.33
21	.81	–15	14	10	–03	14	12	–09	12	10	–01	–09
22	77	–19	.29	.12	.04	01	12	–03	–05	04	–07	–14
23	.63	01	12	.00	.25	15	–07	–07	41	–03	.08	–08
24	.34	–18	.07	40	10	13	.33	–14	–05	.09	–.33	–.30
25	43	–02	04	14	.52	06	11	–03	–13	–09	–.26	–18
26	.35	.06	.52	.08	.22	.26	03	–.04	.07	08	–00	–46
27	.22	.07	75	–02	.07	.01	10	–09	11	.05	–.27	–06
28	72	–10	.25	.07	18	03	.06	–06	–06	–06	–.25	–.28
29	41	.00	.50	19	17	.25	.08	.06	18	02	03	–43
30	.66	.08	.08	.28	18	10	.06	03	–.09	–.08	–.27	–18
31	.52	.21	–01	.24	.28	.06	10	.01	02	.27	–.36	–.23
32	.34	.20	17	–10	–.02	–13	20	–14	.20	–.07	–15	–.56
33	.37	08	.57	.30	.03	.20	12	06	05	04	.06	–.29
34	14	–12	13	.06	08	02	12	–19	.64	.20	–.06	–17

35	.38	14	13	13	01	.37	.07	12	18	10	-.52	-11
36	27	19	.24	.04	19	12	.06	.01	-02	09	-.54	-10
37	.38	12	49	.03	18	17	05	-02	.28	-.21	-.26	-16
38	.13	.24	05	15	61	-01	41	03	26	-04	-.08	-10
39	.26	.08	.27	15	17	.33	01	.07	40	08	01	-.34
40	.30	.05	.09	.04	.30	.62	02	01	01	-.03	-.29	-19
41	.05	12	.37	43	.21	13	18	-.27	.03	.28	16	-11
42	17	.00	44	.50	.21	-04	.26	.00	.21	.06	-18	02
43	11	-13	04	.24	.31	19	45	-06	13	15	-44	-12
44	17	.33	.36	.52	14	05	-01	-07	.20	17	-.27	03
45	.32	.26	.30	.31	-01	.09	16	-01	.03	-19	-18	-.39
46	.45	12	.08	.06	43	-02	.01	-.20	.00	19	-.32	10
47	.20	.25	18	17	.26	00	-01	-.25	13	.37	-.53	-04
48	.04	-03	.34	-.06	15	.27	31	12	.55	17	-13	-14
49	-10	.26	.05	17	.50	11	15	-12	.27	09	-.27	-09
50	13	.08	-08	44	-11	-09	18	-.32	.56	-19	.02	14
51	11	40	.20	-12	06	.02	-04	17	.59	-.04	.04	.01
52	.02	14	.02	15	12	.05	11	07	.21	.69	-19	14
53	14	.06	.03	.36	12	10	.62	.01	18	16	-14	10
54	04	.54	10	.10	04	13	15	-47	01	10	-18	-13
55	.32	-09	.02	.61	03	.06	06	-.04	-03	.06	-.36	-06
56	17	10	47	.23	48	-00	23	-07	.21	-00	-.08	.23
57	.04	18	16	41	17	-03	-.04	-12	.56	04	-13	-17
58	-.24	.24	.25	-14	08	.08	19	-.37	19	.21	-.27	-34
59	11	11	-02	.02	-08	.03	.05	-47	-17	.58	-09	-20
60	18	11	13	.08	-01	78	17	-12	.09	04	-12	.03
61	.28	11	.35	.02	-08	19	.57	07	.26	03	16	-11
62	.53	.01	.04	.26	10	.26	.03	-16	-03	-09	-.49	-08
63	.09	33	.09	04	19	.04	01	-14	08	.54	00	-40
64	.58	10	.52	.06	11	-.07	-.07	-03	18	03	04	11

Appendix IV

Q-fact analysis. Blacky Pictures. Rot ted facto matrix. Db 1–27 Cb 28 54

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Facto														
1	.26	46	07	09	07	.07	.05	11	− 13	− 08	.20	19	− 19	.38	− 01
2	10	14	04	.02	.03	− 12	08	19	− 03	− 07	19	.20	13	64	− 06
3	.03	.31	03	− 07	.22	−.28	08	.53	− 09	04	11	08	02	11	01
4	11	.01	12	10	14	− 05	02	76	− 01	− 09	− 03	.03	07	11	− 12
5	01	.32	−.07	11	.03	−.31	14	.20	−.20	− 06	.57	− 11	− 07	.20	− 16
6	[illegible]	79	.06	15	.03	− 09	− 08	10	− 05	.06	.04	− 05	.05	12	01
7	.01	19	− 06	− 06	19	−.29	.04	17	61	14	18	.08	.20	.23	− 09
8	.02	.09	[illegible]	.24	13	− 09	13	− 08	− 15	− 08	.08	− 12	17	70	− 09
9	02	10	21	.05	− 11	− 47	.26	08	− 14	−.27	.06	17	20	.37	.21
10	−.04	.07	12	.23	00	−.68	− 15	06	− 14	−.02	.05	11	16	.23	− 13
11	35	− 18	.29	.25	08	− 41	10	15	− 00	16	− 10	− 19	18	07	− 27
12	−.05	.03	04	.21	14	− 14	− 08	.01	− 01	− 10	−.04	13	.73	13	− 04
13	.02	.20	.32	− 11	21	−.57	.23	.07	−.32	− 05	08	−.05	.01	03	− 03
14	.25	07	.27	.07	− 10	− 18	.06	11	−.25	− 08	.25	− 05	.60	05	− 04
15	17	06	06	.21	08	04	.06	49	− 16	− 01	.22	.21	.33	33	− 02
16	.25	01	− 04	13	17	−.64	11	14	−.22	− 19	.04	.03	.25	03	03
17	12	.03	71	02	.26	−.06	−.05	.04	− 10	− 04	.08	.06	12	.03	− 12
18	− 16	.22	− 04	.05	.07	− 17	.23	.33	−.23	13	− 10	10	47	05	− 32
19	.04	.20	− 08	.37	.27	−.36	.08	.24	− 11	− 12	− 19	14	14	27	02
20	− 14	10	− 01	.25	17	− 13	− 14	.38	− 40	−.30	− 09	− 09	.00	.24	− 18
21	.23	−.26	13	−.00	.39	−.22	43	.37	− 06	01	10	− 06	23	15	− 00
22	43	− 09	.25	08	10	− 16	14	.22	−.38	− 16	.01	−.08	.05	40	− 02
23	.05	46	.25	−.06	14	− 05	.24	01	− 31	− 16	−.31	18	15	− 08	−.29
24	10	.37	.58	14	01	− 12	19	19	− 08	− 16	19	− 06	− 08	09	− 08
25	.26	.08	− 12	.07	17	−.37	16	.07	15	02	03	08	.51	2	− 23
26	− 08	.26	.20	−.03	40	−.39	14	27	08	−.36	10	11	.07	− 08	− 06
27	− 04	− 06	.01	.07	41	− 33	07	.21	− 06	− 15	.27	07	33	11	− 15
28	−.04	12	08	.09	46	− 44	−.25	− 01	− 11	.23	14	.28	15	19	− 18
29	.23	61	− 02	− 04	30	− 11	.20	− 09	02	− 05	12	17	15	.20	09
30	.27	.29	06	.02	[illegible]	−.33	−.07	15	01	− 18	− 12	13	− 03	.54	− 09
31	.32	− 05	.09	17	[illegible]	− 02	− 11	.36	−.21	−.29	16	06	.33	16	04
32	.20	.21	−.30	.00	.20	−.32	.01	10	01	−.36	.22	.22	07	.22	−.29
33	− 00	− 02	17	.09	12	− 18	04	05	−.28	−.59	09	− 06	18	.32	− 09
34	76	14	.08	12	10	− 05	.06	05	− 05	03	08	03	.04	16	− 13

35	.22	18	.32	44	29	04	−09	.27	−10	18	04	.21	13	16	05
36	.09	.23	.06	.57	00	43	.29	05	−10	−08	.23	.03	06	.07	04
37	10	.04	.20	10	13	−.01	15	−01	−06	−08	71	19	14	06	−08
38	.04	.09	16	44	18	−08	16	15	−14	13	.21	−12	.30	24	−30
39	.01	07	.05	15	.08	−14	16	12	−11	.00	.09	79	15	10	−08
40	08	.01	.20	15	−.04	−11	.21	−03	−.58	−16	.09	14	.04	.03	−16
41	.31	03	.21	.25	.53	.05	30	14	−07	.06	−02	−02	.05	12	−.23
42	11	14	.37	17	.25	−09	−.01	01	−16	−01	02	.24	−02	.05	−.35
43	25	07	05	.54	01	−13	.26	13	.20	.00	.20	.31	.07	−02	−08
44	03	.08	10	.20	15	−.21	.57	09	−04	−.20	15	.27	−13	19	−06
45	10	02	.07	.09	13	−02	09	16	−17	−11	17	−03	.20	13	−74
46	32	01	09	.06	11	−05	14	.22	−06	−36	.05	07	39	−03	−.29
47	08	.05	01	12	17	01	78	−01	12	.04	.09	05	09	.06	−09
48	06	15	.39	11	.03	−.23	12	.52	−06	−07	10	12	01	01	−41
49	.20	13	.01	18	.67	−06	18	12	−12	−10	.04	08	.07	−03	−.20
50	.02	.24	.05	.26	.66	−13	14	.29	06	−09	14	−09	.20	01	01
51	15	.01	.27	05	72	−15	03	08	−10	−.04	−04	09	−06	.21	−06
52	.28	05	02	10	.28	−.28	−01	12	−43	25	−01	12	04	15	−.30
53	18	12	42	−11	.09	−42	16	32	10	−09	−.05	15	18	08	−.29
54	.04	.01	01	71	.27	−01	.07	.01	06	−15	.02	09	.25	17	−.20

Appendix V

Q-factor analysis. Blacky Pictures. R tated factor matrix. Dg 1 32. Cg 32–64

Case	Factor 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	11	13	06	02	02	.00	04	06	–17	00	25	.36	–03	14	–.62	11	–.04	–07
2	13	10	18	05	30	01	29	07	07	–11	–.25	61	–11	–07	–08	04	–.02	08
3	04	08	45	[illegible]	.39	16	01	.36	19	–08	28	–[illegible]	–[illegible]	01	–.23	–07	–15	–06
4	19	16	03	.27	07	12	–12	43	20	–.21	10	20	.23	–08	–.35	.27	.02	10
5	11	07	24	–14	14	–13	31	.35	14	–14	07	–04	–17	23	–43	.21	–15	01
6	22	20	47	–.21	.21	32	02	09	07	–17	–.27	22	–14	04	–11	07	.01	09
7	47	.05	07	.03	14	–.10	28	17	–09	–07	.26	38	00	.28	–10	14	–16	07
8	.08	02	10	–05	.08	.07	13	08	07	–10	16	76	06	05	–.20	11	–16	.09
9	04	.09	11	.83	08	–.03	10	13	02	–04	.07	11	.08	01	–04	01	–.06	13
10	05	.02	19	–.26	05	–04	09	05	10	–73	.04	09	–04	16	–.28	03	.02	05
11	02	02	14	.05	.02	.23	13	12	10	02	16	.08	–04	73	–13	23	11	03
12	.01	.07	10	.03	.07	16	18	05	07	–14	13	08	–75	18	–.09	00	–12	06
13	11	07	03	–05	16	17	16	03	.20	–.24	–16	.01	–11	16	–.66	00	–17	08
14	17	05	.20	–12	08	10	07	60	–02	–09	–.02	12	00	16	–41	05	–.08	12
15	.23	00	19	–09	10	–02	17	.28	–01	–.57	–02	–10	–01	01	.03	31	–.20	11
16	13	19	15	–.36	10	.32	.29	01	03	–.20	04	–04	–02	.53	–16	–03	–12	–01
17	.02	07	–.01	–.27	.20	–10	43	.53	13	–06	.03	14	–18	10	–07	19	–.01	–.06
18	.03	.04	–18	01	10	.06	11	.08	16	–18	–14	22	–.30	.56	–.26	–02	.06	–.7
19	.20	.01	14	–09	10	02	11	14	10	–.08	11	12	–10	10	–09	13	–73	15
20	13	11	15	–.55	.06	12	–13	17	07	–.23	13	14	–42	–00	.01	.23	–16	–12
21	13	–08	03	–.21	–04	.21	06	17	.24	–09	–09	.28	–02	07	13	46	–.27	.06
22	.09	.22	12	–.38	.08	.07	.20	–18	04	–13	10	20	03	.05	–16	.22	–44	06
23	10	12	10	–.29	–.05	11	–04	.24	17	–04	09	.63	–.21	16	–01	01	–06	18
24	.21	.03	46	–17	15	–10	14	06	18	–10	10	.26	–13	–03	–.21	37	–08	04
25	–.1	13	–13	08	15	.27	10	.30	12	–10	.21	.20	16	32	–18	–00	–35	10
6	13	09	03	–14	.22	06	23	–.04	.39	21	.09	.04	–.36	06	–00	.37	–.03	.23
27	13	–17	13	.02	–04	72	19	14	04	–01	14	12	–13	15	–.23	07	–.01	05
28	.20	.07	.08	–01	–.08	.33	–.07	–.00	01	–.20	–.01	15	–18	15	–.33	63	–.06	14
29	–.04	–08	.27	–.38	–10	–.09	–00	.28	10	–11	.05	19	–.25	14	–09	–01	–.35	31
30	72	.08	15	–12	.09	.22	–05	09	12	–.08	04	05	–08	–00	–.20	02	–22	00
31	01	–00	.01	–13	.08	.31	.04	.75	08	–15	.08	16	–04	19	.09	.00	–12	.07
32	.04	.23	.02	–.04	15	.21	10	11	12	–05	.09	.02	–10	10	.08	19	–.05	17
33	12	14	.04	–10	79	07	18	16	–.02	–.08	–.03	12	–.09	10	–06	11	–.06	–02
34	.24	.31	.04	–.35	–01	04	09	14	11	00	20	–.04	14	29	–.38	.25	–12	–04
35	–.04	[illegible]	–.05	.07	.01	18	18	11	13	–.68	.00	18	–.21	09	–06	10	–.05	–.20

36	16	30	01	.07	25	11	16	.08	– 00	33	– 02	– 04	13	.22	– 14	.58	– 14	13
37	.04	06	.27	01	.04	02	.48	.26	.50	.02	10	06	00	23	– 18	10	– 00	– 14
38	30	05	17	03	.28	18	06	05	44	– 11	26	07	– 13	.04	11	02	–.22	.36
39	06	17	08	07	19	14	10	40	13	– 08	06	18	–.29	– 06	–.23	39	–.04	–.25
40	05	31	12	.27	14	12	02	14	.24	.31	– 11	16	–.23	– 12	–.23	09	– 45	– 04
41	.09	10	15	02	70	.21	.34	.23	– 08	.21	.35	14	–.23	–.10	–.23	10	–.22	17
42	05	02	08	–.20	.01	18	10	05	14	–.02	76	09	– 16	12	–.03	–.01	– 09	17
43	20	06	14	– 07	.03	06	11	16	06	14	.01	.06	– 11	68	– 01	– 01	–.39	– 10
44	10	13	74	12	02	.06	17	.02	13	– 09	02	– 12	– 03	.07	01	03	– 13	.03
45	04	.84	10	– 08	11	01	07	.07	03	05	01	14	– 06	10	– 10	04	–.00	03
46	41	.08	.06	01	14	.05	.20	.05	.59	– 08	– 05	08	– 12	– 05	–.38	10	– 00	.04
47	12	.21	.22	.04	06	.20	.31	38	.06	07	– 19	.24	–.29	04	.07	– 03	–.02	.23
48	12	.23	41	00	.06	–.03	.04	11	48	–.34	13	16	– 06	14	.07	03	– 03	11
49	11	02	.08	– 06	08	12	71	11	06	– 10	.07	21	– 12	09	– 14	00	–.09	11
50	18	.21	18	–.02	14	.24	.63	–.06	12	–.29	05	.09	– 04	03	.02	08	–.03	04
51	.06	.28	.39	– 08	–.26	16	.22	14	02	10	.05	.52	– 11	25	.04	04	–.08	– 08
52	.03	02	16	– 09	– 10	10	06	06	73	–.09	04	07	–.03	.20	05	04	– 12	04
53	.20	42	15	– 09	10	09	06	15	18	–.25	11	– 03	– 39	02	–.05	15	.06	.26
54	.03	.08	.03	– 11	–.03	16	08	07	08	.05	13	16	05	01	–.02	11	– 12	78

Db	Factor I ■	Factor IV R	Factor XIV R	Factor III R	Factor III ■■	Factor VI BP	Factor XIII BP	Neurotic index	Cerebrolesional index	Percept dist index	Emotional dist index	Penetration	Barrier	Object relation	Orality	Aggressivity	P anal trait	Ego weakness	Identity index	Emotional lability	School-problems	Peer problems	Aggression	Anxiety index	Wish to get healthy	Worry for the future	Problem in the schoolrefectory	Paroxysmal headache	Paro xysmal abdominal pain	Nailbiting, tics, pavor nocturnus, stuttering	Hypogly. mc convulsions	WISC
1	0	1	0	0	0	0	0	3	1	1	4	2	0	0	0	1	0	0	0	0	1	0	1	1	0	0	0	0	0	1	1	3
	0	0	0	0	0	0	0	1		2	4	2	0	0	0	0	1	0	0	0	1	1	0	1	0	0	1	0	0	1	0	4
3	0	0	1	0	0	0	0	4	3	2	4	2	0	0	0	0	0	0	0	0	1	1	0	2	0	0	0	0	0	0	0	6
4	0	0	0	0	0	0	0	1	3	0	3	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	9
5	0	0	0	0	0	0	0	2	2	2	4	1	0	0	0	0	1	0	0	0	1	1	0	1	0	0	1	0	0	1	1	6
6	0	0	0	0	0	0	0	6	5	0	2	2	1	1	0	0	1	0	1	0	0	1	0	3	0	1	0	0	0	0	1	8
7	0	0	0	0	0	0	0	3	2	0	2	1	2	1	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0	1	1	7
8	0	0	0	0	0	0	0	4	3	3	4	3	0	0	1	1	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	5
9	1	0	0	0	0	1	0	5	2	2	3	0	0	0	0	1	1	0	1	0	1	1	1	3	0	1	0	0	0	1	1	6
10	0	0	1	1	0	1	0	7	5	1	6	2	4	1	0	0	1	1	1	1	1	0	1	4	0	1	1	0	0	1	0	6
11	0	0	0	0	0	0	0	6	4	2	4	1	0	0	0	1	1	0	0	0	0	0	1	3	0	1	0	1	1	0	1	8
12	0	0	0	0	0	0	1	4	4	1	1	0	0	0	0	0	1	0	1	0	1	0	0	3	0	1	1	0	0	0	0	5
13	0	0	1	0	0	1	0	5	4	1	3	2	2	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	6
14	0	0	0	0	0	0	1	2	2	2	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1	1	1	1	7
15	0	1	0	0	0	0	0	5	3	1	0	3	2	1	0	0	0	0	1	0	0	1	0	3	1	1	1	0	0	1	0	8
16	1	0	0	0	0	1	0	3	2	0	2	0	4	0	0	0	1	1	1	1	0	1	0		0	1	0	0	0	0	0	4
17	0	0	1	0	1	0	0	4	2	1	2	0	2	0	0	0	1	0	0	1	0	0	0	4	0	1	0	0	0	0	0	7
18	0	0	0	0	0	0	1	4	2	1	1	0	0	0	1	0	1	0	1	0	0	0	1	1	1	0	0	0	0	0	0	9
19	0	0	0	0	0	0	0	3	4	0	2	1	1	1	0	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	5
0	0	0	0	0	0	0	0		2	0	2	0	3	1	0	0	0	0	1	0	0	0	0	5	0	0	1	0	0	0	0	5
21	1	0	0	0	0	0	0	6	1	0	2	3	3	0	0	1	0	0	0	1	0	1	0	3	1	1	0	0	0	0	1	9
2	0	0	0	0	0	0	0	5	2	1	1	4	0	0	0	0	0	0	1	0	0	1	0	3	1	0	0	0	0	1	0	8
3	0	0	0	0	0	0	0	5	2	0	2	3	0	1	0	1	1	1	1	0	0	1	0	2	1	0	0	0	0	1	1	7
24	0	0	0	1	0	0	0	5		0	1		2	0	1	1	1	0	1	1	0	1	0	4	1	1	1	0	0	0	1	9
5	0	0	0	0	0	1	0	5	2	3	3	3	0	0	1	1	1	0	1	0	1	1	0	2	1	1	0	0	0	0	1	2
6	0	0	0	1	0	0	0	4	4	1	3	1	0	1	0	0	0	0	0	0	1	1	1	2	1	1	1	0	0	1	0	5
27	0	0	0	0	0	0	0	4	3	1	2	2	0	1	0	1	0	0	1	1	1	0	1	2	1	0	0	0	0	0	1	3

Appendix VI. Personality and clinical deviations in the individual cases. Diabetic boys.

School difficulties = teacher's opinion, Peer problems = mother's and/or child's opinion, Aggressivity = aggressive trait in the projective tests, Aggression = aggressive signs revealed by doctor's interview.

Dg	Factor IX R	Factor X R	Factor XI R	Factor XII R	Factor IV BP	Factor VI BP	Factor VIII BP	Factor XIV BP	Factor XV BP	Neurotic Index	Cerebrolesional Index	Perceptual Index	Emotional dist. Index	Penetration	Barrier	Object criticism
1	0	0	0	0	0	0	0	0	1	2	2	0	1	0	0	1
2	1	0	0	0	0	0	0	0	0	4	4	2	2	1	0	1
3	0	0	1	0	0	0	0	0	0	4	3	1	1	2	0	0
4	0	0	1	0	0	0	0	0	0	2	4	0	1	2	0	1
5	0	0	0	0	0	0	0	0	0	4	3	1	2	1	0	0
6	0	0	0	0	0	0	0	0	0	4	2	1	3	2	0	1
7	0	0	0	1	0	0	0	0	0	2	1	0	2	0	0	1
8	0	0	0	1	0	0	0	0	0	1	2	0	2	0	0	1
9	0	0	0	0	1	0	0	0	0	7	2	0	2	2	0	1
[illegible]	0	0	0	0	0	0	0	0	0	4	2	0	1	1	0	1
[illegible]	0	0	0	0	0	0	0	1	0	7	3	1	2	1	0	1
[illegible]	0	0	0	0	0	0	0	0	0	4	3	0	1	2	0	0
[illegible]	0	0	0	0	0	0	0	0	1	2	1	0	1	3	0	1
[illegible]	0	0	0	0	0	0	1	0	0	4	2	1	0	1	0	0
15	0	0	1	0	0	0	0	0	0	6	4	2	4	1	0	1
16	0	1	0	0	0	0	0	1	0	4	4	0	3	2	0	1
17	0	0	0	0	0	0	1	0	0	3	3	0	2	3	6	1
18	0	1	0	0	0	0	0	1	0	6	6	3	1	1	6	1
19	0	1	0	0	0	0	0	0	0	7	2	0	1	3	0	0
20	0	0	1	0	1	0	0	0	0	6	4	1	3	3	5	0
21	0	0	0	0	0	0	0	0	0	5	3	1	1	2	0	1
22	0	0	0	0	0	0	0	0	0	3	4	1	2	4	4	1
23	0	0	0	0	0	0	0	0	0	4	5	2	2	1	0	1
24	0	0	0	0	0	0	0	0	0	3	2	1	1	3	0	1
25	1	0	0	0	0	0	0	0	0	3	4	0	4	2	0	1
26	0	0	0	0	0	0	0	0	0	5	4	1	2	5	5	1
	0	1	0	0	0	1	0	0	0	5	4	0	1	6	7	0
	0	0	0	0	0	0	0	0	0	4	6	0	3	1	0	0
		0	0	0	0	0	0	0	0	5	4	0	2	1	0	1
		0	1	0	0	0	0	0	0	3	4	1	0	2	0	1
			0	0	0	0	1	0	0	4	3	0	1	2	0	1
			0	1	0	1	0	0	0	3	2	0	1	4	0	0

Dg	Orality	Aggressivity	Paranoid traits	Egoweakness	Identity index	Emotional lability	School problems	Peer problems	Aggression	Anxiety index	Wish to get healthy	Worry for the future	Problems in the school/factory	Paroxysmal headache	Paroxysmal abdominal pain	Nailbiting, tics, pavor nocturnus, stuttering	Hypoglycemic convulsions	WISC
1	0	0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0	9
2	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	0	8
3	1	0	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	7
4	0	0	1	0	0	0	0	1	1	2	1	0	0	0	1	1	0	7
5	0	0	0	1	1	1	1	1	0	4	1	1	1	1	0	2	1	5
6	0	1	0	0	0	0	0	1	1	1	0	1	0	1	1	0	1	7
7	0	0	1	0	0	0	0	0	0	1	0	0	0	1	0	0	1	8
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	6
9	0	1	1	0	0	1	1	1	1	4	1	1	1	1	1	1	1	6
[illegible]	0	1	1	0	0	0	0	1	0	4	1	1	0	0	1	1	0	6
[illegible]	0	0	1	0	1	1	0	0	0	4	1	1	0	0	0	1	0	7
[illegible]	0	0	1	0	0	0	0	0	0	2	1	0	0	0	0	0	0	7
[illegible]	1	0	0	0	1	1	1	1	0	2	1	0	0	0	0	1	0	7
[illegible]	0	1	1	0	0	0	0	0	1	1	0	0	0	0	0	1	0	5
15	0	0	1	0	1	0	1	1	0	4	1	0	0	1	0	0	0	6
16	0	1	1	1	1	0	1	1	0	3	0	0	0	1	0	1	1	5
17	0	0	1	0	1	1	1	1	0	2	0	0	1	0	0	1	1	5
18	0	0	1	1	1	0	1	1	1	4	1	1	0	0	0	0	0	4
19	0	0	1	0	0	0	0	1	0	3	1	1	0	0	0	0	0	9
20	1	0	1	0	1	1	0	1	0	3	1	1	0	1	1	0	1	3
21	0	1	0	1	1	1	0	0	1	3	1	0	0	0	0	1	1	6
22	1	1	1	0	1	1	0	1	1	2	1	0	0	1	0	1	0	4
23	0	1	0	0	0	0	1	0	1	1	0	0	0	0	0	1	0	4
24	1	1	1	0	1	1	1	1	1	4	0	0	0	1	1	1	1	7
25	0	1	0	0	1	0	0	0	1	3	1	0	0	0	0	0	0	6
26	1	1	1	0	0	1	0	0	1	3	1	1	0	0	0	1	0	7
	0	1	0	0	1	0	1	1	1	3	1	1	1	0	0	1	0	8
	1	1	0	0	0	1	0	0	1	3	1	0	0	0	0	1	0	5
	0	0	0	0	0	1	0	0	1	2	1	1	0	0	0	0	0	7
	0	0	0	0	1	0	1	1	0	2	1	1	1	1	0	1	0	4
	1	0	1	0	1	1	0	1	1	3	1	1	0	0	0	1	0	5
	0	0	1	0	0	1	0	0	0	2	0	0	0	0	0	0	0	9

Personality and [illegible] deviations in the individual cases. Diabetic girls.

Appendix VIII

R facto analyses. Rotated factor matrix.

Var.	1	2	3	4	5	6	7	8	9	10	11	12	13
1	– 14	– 12	– 06	–.00	–.09	.90	–.01	– 09	.01	–.01	–.01	.08	– 11
2	.01	11	– [illegible]	14	19	–.01	.03	– 79	– 09	.09	– 15	16	15
3	– 15	–.37	19	.28	18	.31	–.27	– 17	.04	– 18	– 19	–.51	– 03
4	–.03	.01	.03	– 05	–.06	–.22	.04	.01	.20	16	– 01	– 77	–.07
5	– 12	–.02	03	–.03	.54	–.06	.32	14	– 11	– 41	–.03	–.07	14
6	– 14	.02	.04	10	.68	[illegible]	04	.06	19	– 17	15	.21	.01
7	–.01	.33	.07	– 07	–.03	–.07	03	–.02	.85	– 00	.08	–.01	18
8	.01	– 08	.04	– 01	–.85	–.05	–.05	– 19	– 02	.23	00	– 16	– 10
9	.00	.20	.07	.04	17	–.05	.09	.22	–.05	–.39	.04	01	–.67
10	.02	.03	.08	.04	09	.05	.04	11	–.06	94	00	– 04	.04
11	02	– 10	– 08	.04	.09	.03	– 08	.02	79	– 04	–.06	– 13	– 06
12	08	– 14	– 78	.07	–.01	.07	.21	17	.02	.09	15	–.20	–.08
13	.00	14	.05	.01	16	77	– 17	–.00	– 05	15	– 08	12	.08
14	–.02	30	16	– 11	19	.57	20	.25	– [illegible]	– 02	.02	.05	–.03
15	– 13	.22	– 15	–.02	.06	–.25	–.41	– 18	–.36	– 04	44	–.24	13
16	– 13	10	–.20	10	– 02	–.01	.02	.01	.08	04	.81	04	– 06
17	17	.09	30	.02	17	.02	01	.09	– 13	–.04	.67	17	09
18	.03	–.04	.24	– 17	.09	.01	–.03	.20	16	– 15	.20	–.05	– 60
19	.91	.06	– 07	– 14	.05	–.02	– 15	– 08	02	– 04	–.09	– 05	–.04
20	.87	12	.07	.06	.02	– 03	– 12	03	03	09	.04	.05	10
21	.09	15	17	–.06	–.07	14	.04	– 76	11	–.20	11	– 10	–.22
2.	–.05	.93	– 00	15	–.03	.07	– 04	– 00	.07	01	–.01	– 02	08
23	.85	–.07	.05	.09	– 14	– 10	12	.05	– 06	08	–.09	03	–.01
24	01	.09	02	.97	.04	–.09	.04	–.02	.04	.01	.04	.04	–.03
25	12	14	– 07	.59	– 17	.30	04	–.00	–.26	.01	11	– 19	.00
6	.85	– 14	00	16	– 14	.07	.07	–.00	– 10	–.09	05	– 07	14
27	.01	10	04	–.07	– 00	.02	05	– 13	07	.32	.20	–.28	–.54
28	75	10	12	–.21	.22	– 03	.01	– 11	14	.05	.04	09	– 41
29	11	02	.28	–.07	.01	–.05	–.83	.05	08	– 19	– 13	09	.00
30	05	93	–.00	15	–.03	.07	– 04	–.00	07	.01	– 01	–.02	–.08
31	01	.09	02	.97	.04	.09	.04	– 02	04	.01	04	.04	–.03
32	.07	40	.22	14	–.09	.09	44	–.39	– 11	– 13	18	– 18	– 10
33	.07	16	– 20	11	– 17	.59	.06	– 17	14	– 11	11	–.23	.22
34	.07	26	– 25	.05	.26	.08	–.08	.26	– 05	–.09	–.20	–.55	.04
35	– 11	14	75	– 04	–.09	–.02	– 13	–.21	–.04	– 19	– 03	.20	.01
36	.03	.07	–.20	– 11	–.09	.24	75	.06	–.02	16	14	16	– 06

Appendix IX

Items included in the R factor analysis

1 Neurotic index
2. Paranoid Traits
3 Cerebrolesional index
4 Object criticism
5 Maladjustment index
6. Perceptual disturbance index
7 Polyphonic potentials
8. Diffuse response to hyperventilation
9 Paroxysmal activity (except 14-6-PS)
10. Alpha frequency
11 Alpha amplitud
12. Emotional lability
13 Reaction to first informatio (mother)
14 Coping with the disease (mother)
15 Degree of control of the disease
16. Tics, nailbiting, etc.
17 Hypoglycemia with convulsions
18 Short in stature
19 School problems
20 Opinion about btained information about the disease (mother)
21 Aggressivity
22. Penetration score
23 Barrier score
24 Egoweakness
25 WISC
26. Social group
27 Duration of the disease
28. Hospitalizations
29 Age at onset
30 No activities together (moth)
31 No physical exercise together with the child (mother)
32. Peer problems
33 Anxiety inde
34 Prefers to have the hild at hom (mother)
35 Identity inde
36 Age

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PÆDIATRICA
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EPIDEMIOLOGY OF SYMPTOMATIC URINARY TRACT INFECTION IN CHILDHOOD

BY J. WINBERG, H. J. ANDERSEN, T. BERGSTRÖM,
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ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 252, 1974

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EPIDEMIOLOGY OF SYMPTOMATIC URINARY TRACT INFECTION IN CHILDHOOD

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H Larson and K Lincoln*

UPPSALA 1974

Aided by the Swedish Medical Research Council, Project No. 19X 765

Almqvist & Wiksell Uppsala 1974

Demographic studies of urinary tract infections (UTI) have been concerned almost exclusively with *asymptomatic bacteriuria* detected at mass examinations of a population (4 26 31 38 45) Our knowledge of *symptomatic* UTI is based on studies of selected populations. Such studies have furnished valuable clinical data, summarized in excellent reviews for instance (30 36 44 46 49 51), while the epidemiologic aspects have been less observed.

In the present study we describe a population of children who presented with a symptomatic [1] apparently primary attack of UTI during a seven-year period The children were drawn from a defined population. Selection factors operating before admission to hospital were probably not very strong. The patients were followed prospectively Data concerning the natural history of their UTI are given with special reference to scar formation and to appearance of recurrences The investigation outlines the medical needs of these patients and suggests working hypotheses for future research on the pathogenesis of UTI Earlier publications (1 2, 3 5 6 7 8 9 10 22 33 53 56 57) based on this material include detailed bibliographies references have therefore been limited to a minimum

POPULATION

Göteborg, a town of about half a million inhabitants has only one paediatric clinic, which is situated at the Childrens Hospital Only a few paediatricians practise outside the hospital Most children with acute illness are therefore taken direct to the outpatient clinic of the Childrens Hospital The annual number of acutely ill cases increased during the study period The staff of the department also examines all newborns in the two maternity units in the town. The primary material of this study (see below) which consists of children examined and treated at the Childrens Hospital and the two maternity units, may therefore be regarded as unselected

The annual number of live births in Göteborg 1950–1966, is given in Table 1 A The incidence of UTI is based on figures given in Table 1 B

MATERIAL

The material consisted of 596 consecutive primary cases of UTI examined and treated at the Childrens Hospital or in the maternity units from 1st January 1960 to 31st December 1966. The ages ranged from the neonatal period to 16 years all children were residents of Göteborg none had had previous symptomatic infections as revealed by the history taken patients with anomalies of the external genitalia, neurogenic disturbances of the bladder or other forms of obstructive uropathy were excluded Vesico-ureteric reflux was not regarded as an obstructive malformation. In "bladder neck obstruction the obstructive element is often difficult to evaluate (27) our judgement in these cases will be presented The

[1] Here "symptomatic" denotes that the child' symptoms were such that the parents sought medical advice

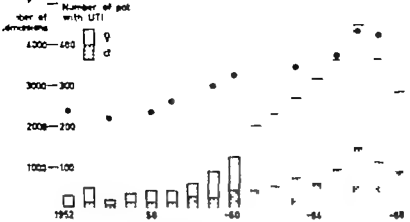

Fig 1 Annual number of hospitalized children and ratio between male and female UTI. Department of Paediatrics, Göteborg.

number of patients with obstructive uropathy during the study period was recorded

The total number of children hospitalized in the years 1952–1968 and the number with UTI are given in Fig. 1 The changes in the number of patients with UTI up to 1966 are probably attributable to increased awareness of UTI During 1967 and 1968 improved organization of the out-patient service probably reduced the number of hospitalized patients. It is our impression that the findings up to 1966 are more or less representative of for Sweden as a whole

METHODS

Diagnostic methods and criteria, as well as the procedures used at follow-up have been described in detail elsewhere (6 9 34 54) The methods of treatment used and the implications of drug-induced changes in gut flora have recently been summarized (33 55) The methods used remained unchanged throughout the course of the study Medical advice was readily available to all patients in this study and we tried to examine them whenever they had symptoms

DEFINITIONS

Urinary tract infection (UTI) infection regardless whether localized to the renal parenchyma renal pelvis bladder or urethra.

Primary infection initial infection onset infection or primary attack of an infection, an infection in a patient with no earlier symptoms or signs of such an infection, as revealed by history-taking

Recurrence a second attack regardless whether reinfection or relapse

Reinfection. a new infection of the urinary tract appearing after the healing of a preceding one demonstrated either by a change of the bacterial species or of the serogroup of the infecting bacterial strain between two consecutive infections Two or more negative cultures between two infections caused by identical strains may also indicate reinfection.

Relapse recrudescence of a preceding infection which had never healed

Pyelonephritis infection of the renal parenchyma Usually indirectly demonstrated

by a *transitory* decrease in the renal concentrating capacity or a *transitory increase of the E coli* antibody titre usually with associated rise in body temperature.

Cystitis an infection localized distal to the kidney (usually in the bladder?) The diagnosis requires normal concentrating capacity *E. coli* antibody titre and erythrocyte sedimentation rate. The condition usually occurs in the absence of a rise in body temperature

Obstructive infection infection associated with stenosis somewhere between the pelvic ureteric junction and the urethral orifice or associated with stones with diverticula, ureterocele or neurogenic bladder Reflux was not regarded as an obstruction

Epidemiological data Definitions given by Larsson (32) *Exact age* (=age next birth day) is used in tables and diagrams.

Neonates infants below one month of age.

RESULTS WITH SELECTED COMMENTS

Annual morbidity 1960–1966

The annual rate of admissions to hospital for primary UTI is given in Fig. 2. The steep increase from 1963 to 1964 was seen in most of the subgroups (5 7 8) The cause of this increase is debatable. Population size did not increase (Table 1 A) and the diagnostic procedures and criteria used in 1959 were not modified during the period of study Increased awareness of UTI was the most likely contributory factor The morbidity risk should thus preferably be calculated from data from 1964–1966 rather than from the whole observation period

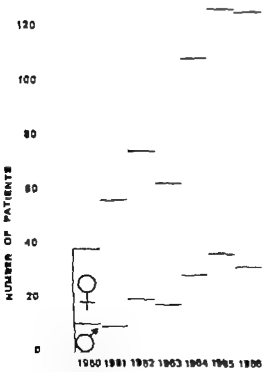

Fig 2 Admission with an apparently primary UTI during 1960–66 The steep increase from 1960–63 to 1964–66 was due to increases in most age subgroups and in both sexes.

The incidences given below are minimum values The extent of the underestimation is unknown, but since the numbers of new cases diagnosed in 1964 1965 and 1966 were virtually the same, the detection rate had presumably approached a maximum level Figures for patients above say 11 years of age may be less reliable than those for younger ones because some of them may have sought advice outside the Childrens Hospital. The calculation of incidence of UTI is therefore based solely on patients less than 11 years old who developed symptomatic UTI between 1964 and 1966.

Incidence of non-obstructed symptomatic UTI

The age distribution of the whole material is given in Table 2. During the period 1964–1966 altogether 90 boys and 252 girls below 11 years of age developed UTI.

The aggregate morbidity risk for boys up to 11 years may with sufficient accuracy be calculated as

Table 1

Year	Live births
A. *Number of li births in Göteborg 1950-66*	
1950	5 774
1951	6.561
1952	5 463
1953	5 686
1954	5.653
1955	5.807
1956	5 947
1957	6.236
1958	6.139
1959	5.960
1960	5.861
1961	6 139
1962	6.181
1963	6.570
1964	7 091
1965	7.016
1966	6.961
B *N mber of children below 11 ears of age residing in Göteborg on December 31 1964-66*	
1964	61.285
1965	61.622
1966	61 731
Total	184 638

$$\frac{90}{184\,638 \quad 2 \quad 11}=\frac{90}{8\,392}=0\ 011 \text{ or } 1\ 1\%$$

and for girls

$$\frac{252}{184\,638 \quad 2 \quad 11}=\frac{252}{8\,392}=0\ 030 \text{ or } 3\%$$

If newborns were excluded the aggregate morbidity risk would be 55/8 392=0 007 corresponding to approximately 0 7% for boys and 235/8 392=0 028 corresponding to approximately 2.8% for girls

Table 2. *Presence of fever ≥38°C according to sex and age at primary infections (neonates excluded)*

	Girl		Boys	
Age-group (years)	Total number	Per cent with fever	Total number	Per cent with fever
$^1/_{12}$–1	1 4	100**	6_	89*
1–3	87	75	9	56
3–10	178	63	22	36*
10–16	30	53	11	77
Total	419		104	

** Sex difference χ^2 $p<0.01$ Sex difference χ^2 $p<0.05$

Age sex and seasonal distribution of primary infections

The ages at onset are shown in Fig. 3 and 4 The relative risk of children developing the disease in different age periods has been calculated from these data (Fig. 5) The approximate female/male ratios for the different age groups in Fig. 5 were 0 4 1.5 4 10, 9 2. The morbidity risk with increasing age seems to decrease more rapidly in boys than in girls. The disappearance of the morbidity risk might be interpreted in different ways as will be discussed later

The onset of infections was evenly distributed over the year Fig. 6. If upper respiratory infections predisposed to urinary infections one would have expected more cases during the winter season. Two earlier studies (40 50) have given contradictory results

Symptomatology

The symptomatology varies with age and sex and has been reported in detail for this material (5 6, 7 8 9) Almost all infants had fever except neonates of whom only 42% had After the first year of life fever became less common (Fig. 3 Table 2) It was significantly less common in males than in females (5)

The high frequency of fever in infants has at least two implications First pyrexia in the patients in this study was associated with a transitory decrease in renal concentrating capacity (7 56) and a transitory increase in *E coli* antibody titre (2 54) suggesting renal involvement The great majority of infections in infants and toddlers should thus be classified as pyelonephritis Second it is noteworthy that 'failure to thrive often held to be a typical manifestation of infantile UTI was rare in this material Since primary infections are usually attended by fever while recurrences or long standing infections are not it is possible that

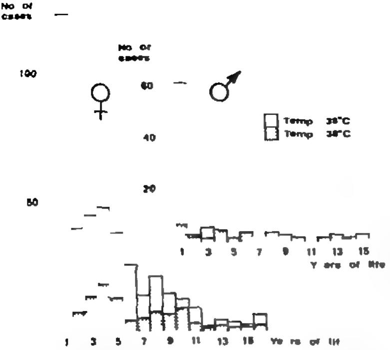

Fig 3 Apparently primary onset of UTI in 419 girls and 104 boys between second month and 16 years (neonates 0–30 days excluded). The proportion of non-febrile infections was very small during the first year of life, but increased with age. Afebrile infections usually associated with micturition disturbances were more common in males than in females (cf 5).

"failure to thrive" is a sign of a neglected or undiagnosed long-standing infection rather than an early presenting symptom.

Bacteriology

Table 3 shows the bacteriological findings in the children arranged according to age and sex. Four features are noteworthy. First, the high frequency of *Proteus* infections in boys over the age of one year, the greater variability of infecting organisms in boys than in girls of the same age (5). Secondly, staphylococcal infections were limited to prepubertal and pubertal children of both sexes, and in girls they constituted one-third of all infections above the age of 10 years (22). Thirdly, in neonates *E. coli* was a significantly less common cause of UTI in the females than in the males. Fourthly, *Klebsiella-Enterobacter* caused 11% of the neonatal infections but were uncommon in older children. If infections reach the urinary tract by the ascending route, the findings would imply that the environmental conditions in the periurethral region and the host defence mechanisms vary with age and sex.

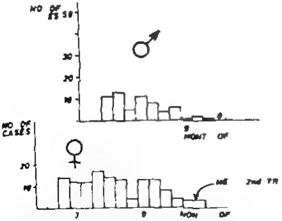

Fig 4 Apparently primary onset of UTI in males and females during the first year of life. Neonates denoted by broken line. The susceptibility to infection may decrease faster in boys. The average number of cases per month during the second year of life was 3.2 for girls and is indicated. For boys it was 0.25.

The *E. coli* O-antigen groups found in different clinical types of infection are given in Table 4. In the girls the common O-groups were found less often in recurrences than in primary infections. This might have been due to acquired immunity or to selective pressure on the gastrointestinal bacterial reservoir produced by use of antibacterial agents (55).

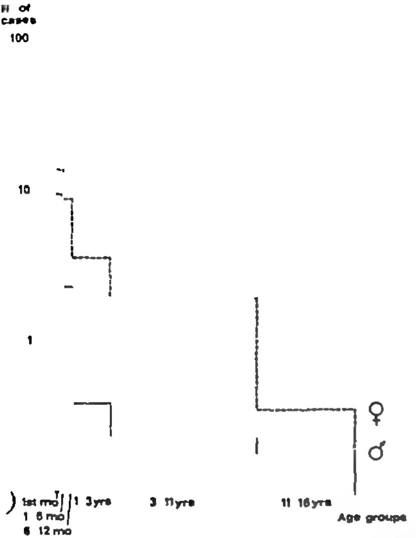

Fig 5 Mean number of new cases per month in different age groups in males and females.

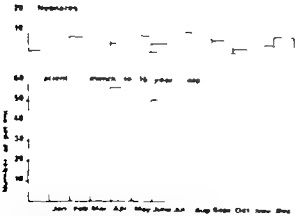

Fig 6 Seasonal distribution of onset of UTI in neonat and in older patients. No differences wer found in these groups, or after di ision of the material nto maller group according to age and sex.

Radiological findings

Occurrence of obstruction During the seven years 174 males were seen with apparently primary UTI In 18 (10 3%) the urinary flow was obstructed (Fig. 7) owing to proven (3 patients) or suspected (2 patients) urethral valves to bladder stone or diverticula (2 pa tients) or to ureteral obstruction (11 patients) (cf 5 7 8)

The frequency of obstruction in girls during the study period is not known but roentgen examination of 144 consecutive girls admitted because of primary infection or a first recur rence (Fig 7) revealed obstruction in three that is 2 1% for details see (56) The differ ence in frequency of obstruction between boys and girls was significant (X^2 p<0 01)

Table 3 *Bacteria isolated at primary infection in relation to sex and age*

Bacteria	Neonates of both sexes (N=73) (%)	Girls 1/12–10 yrs* (N=189) (%)	Girls 10–16 yrs (N=30) (%)	Boys 1/12–1 yr (N=62) (%)	Boys 1–16 (N=42) (%)
E. coli	75	83	60	85	33
Klebsiella	11	<1	0	2	[illegible]
Proteus	0	3	0	5	33
Enterococci	3	2	0	0	2
Staph. albus	1	<1	30	0	12*
Other bacteria	4	<1	0	3	2
Mixed etiology	4	1	3	2	5
Unknown	1	9	7	3	10

No differences between girls 1/12–1 and 1–10. No differences between boys 1–10 and 10–16 except for *Staph. albus* see footnote.

Four of the five patients were above 11 years of age.

57 % in girls and 83 % in males. This difference is significant (p=0.016).

Obstruction was thus uncommon in this unselected material and could not explain the high frequency of recurrent infections and of primary UTI during infancy. Though uncommon obstruction is very important because it can lead to progressive renal damage.

Narrowing of the bladder neck demonstrated by micturating urethro-cystography was common in the males below the age of one year, uncommon in older boys and rarely if ever seen in the females. The frequency decreased with increasing age (Table 5) and in longitudinally followed cases the 'narrowing' tended to disappear spontaneously (Fig. 8).

Two of the 22 infants with such 'narrowing' were operated upon. In both cases the operation was followed by several recurrent infections. A third patient was examined on various occasions with endoscopy and micturating urethro-cystography. These examinations were usually followed by infections which were sometimes severe. This experience led us to be more conservative in such cases, especially as a 'narrow' outlet if left untouched was not associated with an increased tendency to recurrence of UTI.

Duplication

Seven (5%) of 146 boys and 28 (12%) of 243 girls had duplication of the upper urinary tract (bifid renal pelvis or complete or incomplete duplication of the ureter) when examined radiographically (Fig. 9). This sex difference was significant (X^2: p<0.05). All the boys were examined roentgenographically at the primary infection but only one-third of the girls were

Table 4 *Per centage distribution of O-antigen groups in E. coli strains found in various clinical types of infection*

	Primary male and female neonatal infections (N=46)	Primary male infantile infections (N=38)	Primary female infections (N=119)	Recurrent female infections (N=72)	Neonatal asymptomatic (ascending?) (N=8)
E. coli O-groups 1, 2, 4, 6, 7, 8, 18, 75	70	76	74	47	25
Other O-groups	24	6	23	45	75
Spontaneously agglutinating	6	18	1	8	[illegible]

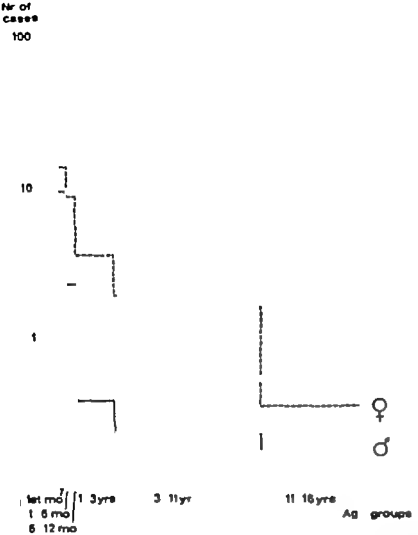

Fig 5 Mean number of new cases per month in different age groups in males and females.

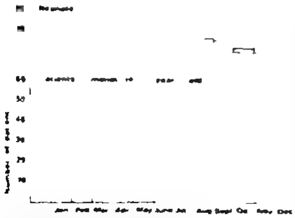

Fig 6 Seasonal distribution of onset of UTI in neonates and in older patients. No differences wer found in these groups or after division of the material into smaller groups according to age and sex

Radiological findings

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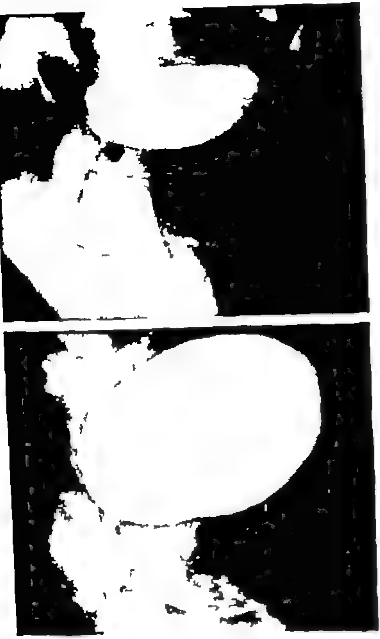

Fig. 8. Patient H. 660801 male. MCU at 4 weeks and at 6.5 months, lateral views. The narrow outlet became wider spontaneously. Similar findings on frontal views.

gests that these lesions were of post natal origin.

The damage was progressive in 22 (58%) of the 38 patients, i.e. in one-fourth of the boys and in three fourths of the girls. The lesions filled Hodson's criteria for renal scarring (24). It is noteworthy that this progression occurred despite the early diagnosis, rapid eradication of the infection and a thorough follow-up with treatment of recurrences. It is a disheartening thought that we do not know how much—if at all—this program altered the natural course of the disease and what the late results would have been without this program.

Results of therapy

Therapy (short-acting sulphonamide sulfisoxazole=Gantrisin®) whether given for 10

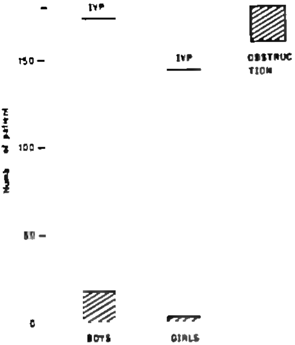

Fig 7 Occurrence of obstruction in 174 apparently primary infections in boys and in 144 first or second infections in girls with a primary onset between birth and 16 years cf text.

X-rayed at this time the remaining two-thirds being examined after subsequent infections If duplication predisposes to recurrences the difference in X ray policy might explain the difference in the observed frequency of duplication. *The films of 129 girls X-rayed at their first* infection were therefore examined for duplications Thirteen (10%) had a duplication The tendency to female overrepresentation persists but the sex-difference is not statistically significant (X^2 $p>0.05$)

The frequency of duplication of the collecting system in the general population is 0 2 to 0.7% more commonly found in females than in males (cf 11 17). Provided that definition of duplication is comparable, the frequency of duplication in our material was roughly 10–20 times greater than in the general population However patients with a bifid renal pelvis with one common ureter are probably not included in the frequency figures given for normal populations while such anomalies are included in our figures This would tend to reduce the difference between expected and found frequency

The association between recurrence and duplication was less obvious. It was seen in 6 (46%) out of 13 girls with duplication and in 34 (29%) out of 116 without (X^2 $p>0.05$) In the girls there was a conspicuous association between progressive scarring and duplication (25)

The nature of the possible association between duplication and infection is uncertain. In general terms urodynamic factors seem to be of great importance for occurrence and persistence of UTI (41 42) They might play a role in this context (52) Another possible explanation for the association could be the suggested increased frequency of renal dysplasia in cases of duplication (13 14) A third possibility could be that, once established infection for some reason produces symptoms more often in patients with duplication However Kunin (31) found 4.5% double collecting system in his survey of asymptomatic bacteriuria.

Scarring

A defect of the renal parenchyma was demonstrated in 18 (13%) of 156 boys and in 20 (4.5%) of 440 girls (Fig. 10) Of these 38 patients clubbing of one or more calyces with or without a corresponding defect of the renal outline, was seen even at the first investigation in one-third—in 3 out of 16 falling ill during the first year of life and in 12 out of 22 falling ill after the first year (X^2 p 0 05) This sug

Table 5 *Narrowing of the bladder neck in males in relation to age at onset of primary infection*

Age at onset of infection (years)	Number of micturating urethro-cystographies	"Narrowing" of bladder neck	Suspected narrowing
Neonates	38	15	4
$^{1}/_{12}$–1	52	7	0
1 16	34	0	2

Table 6 *Result of 10 days sulphonamide therapy*

A=main material, B=in 20 girls with many recurrences

	Neg. culture after 10 days treatment[a] (%)	Pos. culture after 10 days treatment (%)	Reinfection rate among those positive at 10 days
A. 396 primary infections	97	3	11/13[b]
B. 88 recurrences in 20 girls	86	14	8/12[b]

[a] Urine obtained at least 60 hours after withdrawal of therapy
[b] Denominator denotes number examined, numerator number with bacterial change.
Of 33 patients in group A with "first recurrence" discovered later than 10–13 days after institution of therapy 28 had proven reinfections. There were similar findings in group B.

the primary infection were rare. In the girls however recurrences often continued to appear for many years.

Epidemiology of recurrent infections with special reference to girls

This was analysed in a material of 419 girls who had their primary infection after the newborn period, and who were observed for a mean of 45 months.

No correlations were found between the risk of recurrence and presence or absence of fever or the age at onset of the primary infection (Fig. 11, Table 8). Since fever in an apparently primary infection probably indicates pyelonephritis and absence of fever an infection confined to the bladder, pyelonephritis does not seem to predispose to recurrences any more than does cystitis. This is in good agreement with the finding that the cure rate at 10 days was similar in all subgroups. Infants did not seem to be more prone to have recurrences than did older girls.

Table 7 *Results of urine culture in 300 episodes of suspected recurrences associated with fever and/or micturition disturbances*

Bact./ml	No
>100 000	270
30–70 000	5
10–30 000	4
< 10 000	21

All with pyuria.

The overall recurrence rate in the 419 girls was 40%. Of the first 243 patients in this series 71 (29%) had a recurrence within one year.

In a sample of 123 patients with their onset of infection before 11 years of age and with at least one recurrence, we analysed in detail when the first recurrence appeared. The age at onset of the primary infection in this sample corresponded roughly to that of the total material. Thus 29% started during the first year, 22% during the second and third, and 49% between 4 and 11 years. The result of the analysis is shown in Fig. 12. Approximately two-thirds of

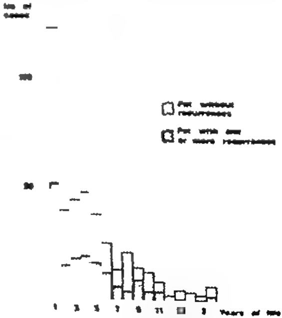

Fig. 11. Risk of recurrence in relation to age at onset in 419 girls. Mean follow-up time 45 months.

Table 8 *Recurrences in relation to age and rectal temperature at primary infection in 419 girls 2 months–16 years*

	With fever			Without fever			
Age group (years)	Total	With recurrence	(%)	Total	With recurrence	(%)	Mean observation time (months)
$1/_{12}$–1	123	53	43	1	0	0	46
1–3	65	24	37	22	9	41	45
3–11	119	51	43	68	27	40	47
11–16	10	3	30	11	1	9	21
Total	317[a]	131		102	37[a]		45

Mean observation time 45 months
131/317 vs. 37/102, difference not significant.

the recurrences appeared within one year Of these 54% appeared during the first 3 months and 46% during the following 9 months. During the following years the risk gradually decreased Eight per cent had their first recurrence more than 4 years after the primary infection This figure is substantially higher than the risk of getting a primary infection which was 3% up to the age of 11 years Thus increased susceptibility to infection persists for many years but as shown in the figure, it does not always manifest clinically

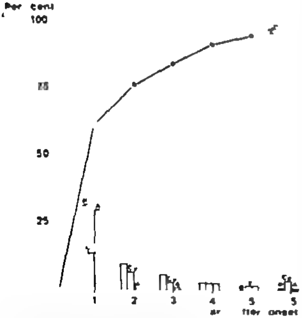

Fig 12 Appearance of a first recurrence after the primary infection, studied in a sample of 123 girls with at least one recurrence Bars denote main symptom F febrile infection CY=afebrile symptomatic infection A=asymptomatic infection.

About one-third of the recurrences were asymptomatic (Fig. 12) The significance of these recurrences is unknown but some may be associated with progressive renal damage (3 53) MacGregor (36) has in a review pointed out the silent nature of chronic pyelonephritis— pyelonephritis lenta If asymptomatic recurrences are to be detected and treated the patients should be followed at relatively close intervals during the first few months after a primary infection The duration of such a follow-up depends on the resources available. The predisposition to infections may persist for decades Lindblad & Ekengren (35) found that out of 18 small girls with UTI who became pregnant later in life 7 (39%) had a symptomatic UTI during pregnancy

Of the above-mentioned sample of 123 patients 41 had their first recurrence within 3 months 35 during the fourth to twelfth month and 18 during the second year after the primary infection The risk of a second recurrence to appear within one year of the first recurrences in these cases was 54 60 and 44% respectively The differences between these figures were not significant Thus the interval between the primary infection and the first recurrence is not a measure of the risk of subsequent recurrence

The risk of a repeated infection within one year of the preceding one was calculated in patients with one two and three earlier infec

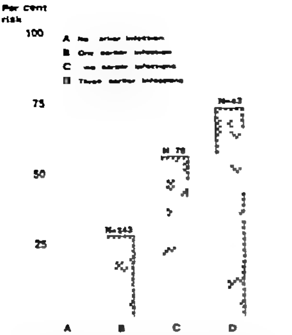

Fig 13 Recurrence rate within one year of a preceding infection related to the number of earlier infections. (A) Approximate risk of 30-day-old healthy girl to have an infection before 11 years of age. (B) Observed risk in 243 girls with one earlier infection. (C) Observed risk in 76 patients with two earlier infections. (D) Observed risk in 43 patients with three earlier infections.

tions (Fig 13) The risk figures should be compared with the risk of a healthy girl to fall ill between the age of 1 month and 11 years of age, which is 2.8% (Fig 13) (A study of the prognosis in patients with four five or more previous infections was precluded by the long-term prophylaxis often received by such patients)

The analysis indicated that the risk of a recurrence increased with the number of preceding infections Since recurrences are mainly reinfections and not relapses, it would appear that there are different grades of susceptibility and that a postulated defect of the defence mechanism is graded It was also observed that recurrences sometimes appeared in clusters separated by long periods of freedom from infection This variability of the recurrence pattern suggests that the resistance to infection varies from time to time

The association between reflux and susceptibility to recurrence was studied in 55 girls with an apparently primary infection or a first recurrence (57), in 47 neonates (5) and in 52 boys 2–12 months old at the primary infection (7) The methods of grading reflux have been described elsewhere (57) The grading differs slightly from that of Smellie (47) No significant correlation between reflux and susceptibility to recurrence was demonstrated It should be mentioned, however that in these unselected populations the number of patients with grade IV reflux was small.

Reflux was more often seen in neonates and infants than in patients over the age of one year (Table 9) The risk of recurrence on the other hand was not greater in the younger agegroups than in the older ones (Table 8) This strengthens the belief that reflux has little influence on the susceptibility to infection. This finding agrees with the controlled study of Govan et al (19)

The results of the analysis of recurrences may be summarized as follows The risk of a recurrence is greater for girls of any age (except neonates) than for boys below one year The risk of a recurrence is greatest during the first few months after a previous infection In patients who have had one infection the risk of later infections is many times greater than the risk of a primary infection in healthy controls. The risk seems to increase with each new infection No correlation was found between risk of recurrence and age [illegible] of infection or reflux

Table 9 *Presence of reflux in relation to age at first infection*

Patient group	No. with MCU	Per cent with reflux
Neonates	47	47
Males		
2nd–12th month	52	30
2nd–16th year	34	18
Females		
3rd–12th month	14	57
2nd–16th year	41	32

GENERAL DISCUSSION

This paper gives approximate figures for the incidence of primary symptomatic UTI according to age and sex The aggregate morbidity risk up to age 11 was at least 3 0% for girls and at least 1 1% for boys

Most authors agree that symptomatic UTI are most common during the first year(s) of life (cf 46) This investigation furnished more precise information on frequency age and sex distribution because the population from which the patients were drawn as well as selection factors operating before admission were under fairly good control This also permitted more reliable conclusions concerning variability of symptoms etiology and frequency of malformations scarring and recurrences with age and sex

Of those who fell ill before 16 years of age the primary infection started during the first year of life in three-fourths of the boys and one-third of the girls The decline in morbidity with increasing age started already during the first year (Fig 5) This might exclude faecal soiling as a main factor in the pathogenesis of UTI Some authors believe the age of predilection to be 3–5 years or more (cf 16 46) This suggestion is probably incorrect but might be explained by an increase with age in the frequency of micturition disturbances as leading symptom (Fig 3)

The bacteria causing UTI *are the same* as those dominating the normal faecal or periurethral flora. Although the virulence of the strains may vary there is little evidence of special uropathogens When usually non-pathogenic bacteria infect patients with weakened resistance such as during immunosuppressive treatment in immunodeficiency or in weak geriatric patients the infection is said to be endogenous or opportunistic Since bacteria found in UTI are commensals and since susceptible individuals seem to have a weakened resistance it seems appropriate to include UTI in this group of infections

It was a remarkable finding that although the original material comprised 156 boys and 440 girls the sex distribution of scarring was roughly equal—18 and 20 respectively

The origin of renal scars seen at autopsy in adults has been the subject of much debate Freedman and Kleeman who studied this in detail (18 28) pointed out three important facts (i) although UTI are much more common in females "scarring is seen equally often in both sexes at autopsy" (ii) these patients often lacked a history of UTI and (iii) lesions histologically indistinguishable from post infection scarring may be caused by a varitey of noxious stimuli particularly vascular lesions and drug toxicity (17 21) They therefore concluded that the role played by infection in the etiology of scarring seen at autopsy was over estimated (18 28) Three things in the present study may weigh against these conclusions. (i) The sex ratio of the living children with parenchymal lesions was the same as in the adult autopsy material (ii) Our study concerned an age-group where vascular disease or drug toxicity can hardly have played any part in the pathogenesis of the renal lesions (iii) 75% of the male infections occurred in children below 1 year and hardly ever recurred after the age of 18 months Also a large proportion of the female infections occurred only during infancy This might explain why adult patients *with renal scars especially males do not present* a history of earlier UTI Thus the objections raised against infection as a main cause of scarring seem to be weakened by the findings in the present investigation A detailed analysis and discussion of this material will appear later (25)

The girls had a high frequency of recurrences for several years after their first symptomatic UTI whereas small boys ceased to have recurrences when one year had elapsed after the primary infection The boys who apparently had their first infection between one and 16 years of age differed from boys falling ill before one year of age in at least two respects They

often had a parenchymal kidney damage with calyceal clubbing even when first seen and they were more prone to recurrences They might constitute a group in whom the really primary infection had escaped diagnosis Scrutiny of records from well baby clinics revealed poor weight gain during early infancy in some of them, which might indicate early infections (5)

As mentioned above urinary infections often continued to recur for many years in the girls but not in the boys At least one-third of these recurrences were asymptomatic At mass examinations of schoolchildren asymptomatic bacteriuria is about 30 times more common in girls than in boys (31 38) The relation between symptomatic UTI and asymptomatic infections diagnosed by screening is uncertain but the above observations would be in line with the view that asymptomatic bacteriuria represents a stage in the course of symptomatic UTI Kunin et al (31) expressed the same opinion The frequency of scars is high in both conditions (4 31 38). Why some patients enter the group of asymptomatic bacteriuria, while others continue to have symptomatic infections is unknown One mechanism which might render a symptomatic infection asymptomatic was proposed by Hanson et al (20 43) who found that the antigenic properties of infecting bacteria were modified during long-standing infections possibly by local antibody production

The high morbidity risk in young age groups and the subsequent decline may be interpreted in different ways We feel that there are three main possibilities which may alone or together explain the shape of the curve in Fig. 5 First a successive maturation of defence mechanisms second a successive elimination of a predisposing factor· third the successive disappearance of the risk of onset may at least partially be an *artefact* If 400 newborn girls are predestined to fall ill before the age of 11 years and one third of them have the disease during the first year this will leave only two-thirds for the remaining 10 years one-sixth of these will fall ill already during the second year and so on This would give a curve resembling those in Figs 3 and 5 This would presuppose that only part of the population is susceptible to UTI. The shape of the curve might be a clue to the pathogenesis of UTI

The epidemiology of recurring UTI was described in detail and commented upon above It was concluded that there are different levels of susceptibility to infection. The great majority of the population is perhaps not susceptible Evidence for this theory has been produced by McCabe & Jackson (37) If only part of the population is susceptible something must differentiate it from the rest. The nature of such a factor is unknown but it may be an inherited one Kunin reported the familial occurrence of asymptomatic bacteriuria (31) We have seen many instances of UTI in mothers and daughters but to our knowledge the hypothesis of inheritance has not been tested

One major objective of future research should be to find methods for identifying susceptible individuals Such an attempt has been made by Stamey et al (48) who examined the perineal flora and compared the findings in adult women with and without susceptibility to UTI

SUMMARY

1 The material consists of 596 consecutive cases of primary (first onset) urinary tract infections appearing from birth up to 16 years of age and which were examined and treated at the Childrens Hospital in Göteborg. The infections occurred during a seven-year period within a defined population The circumstances under which the study was conducted suggest that most symptomatic infections occurring during the study period and for whom

the parents sought medical advice were notified

2 The total morbidity risk at 11 years of age of symptomatic UTI was 3 0% for girls and 1 1% for boys These are minimum figures The morbidity risk is highest during the first month of life and then decreases more rapidly in boys than in girls

Possible interpretations of the reason for decreasing risk with increasing age of falling ill with a first infection are suggested The male/female ratio starts at 2.5 1 during the first month and then successively changes to 1 20 There was no seasonal variation of the time of onset in either sex

3 Presentation with fever was most common in the first year after which it slowly decreased Failure to thrive was a rare symptom Certain other age and sex differences in presenting symptoms were recorded Most infections within the first year of life probably involved the renal parenchyma

4 The etiology varied with age and sex If infections reach the urinary tract by the ascending route this could indicate differences in the environmental conditions in the periurethral [illegible] may be a clue to a better understanding of the pathogenesis

5 Obstructive malformations were found in 10% of boys and 1–2% of girls and cannot explain the high frequency of early infantile infections in either sex

6 Narrowing of the bladder neck was common in males during the first year of life the frequency declining with age It disappeared spontaneously during follow-up of individual cases and was not regarded as an obstructive malformation

7 Duplication of the collecting system was seen in 10% of girls and in 5% in boys which is more than expected The cause and nature of the association between infection and duplication are not known

8 In 13% of boys and 4.5% of girls a reduction of the renal parenchyma was seen either at the first investigation or developed later probably owing to infection. Although UTI was more frequent in females than in males the total number of patients with parenchymal damage was equal in both sexes even during childhood In boys the kidneys might be more vulnerable than in girls

9 The immediate cure rate after 10 days therapy was 97% Recurrences were usually reinfections

10 Recurrent infections were often difficult to diagnose Pyuria and symptoms of UTI were associated with insignificant bacteriuria in 10% (30 of 300) of suspected recurrences

11 Susceptibility to recurrence was studied in relation to various parameters Girls were at greater risk than boys, and the risk was in both sexes greatest during the first 2–3 months after a previous infection Boys rarely had a recurrence more than one year after the primary infection while girls often continued to have recurrences for many years The risk seemed to increase with the increasing number of previous recurrences No correlation was found between the frequency of recurrences and age at onset of primary infection or with symptomatology etiology reflux or duration of therapy

12 The risk of recurrence was many times greater in a patient who had had one infection than in a previously healthy patient The possibility that the degree of susceptibility to UTI might depend to some extent on genetic factors should be examined

ACKNOWLEDGEMENTS

We thank Mrs Ruth Engström Göteborg for very competent secreterial work during many years Dr Tage Larsson Skandia Life Insurance Company Stockholm, for stimulating discussions and advice concerning epidemiologic problems, and Dr A W Asscher K.R U F Institute of Renal Disease Royal Infirmary Cardiff for valuable criticism of the manuscript

REFERENCES

1. Andersen, H. J Clinical studies on the antibody response to *E. coli* O-antigens in infants and children with urinary tract infection using passive haemagglutination technique. *Acta Paediat Scand*, Suppl. 180 1968
2. Andersen, H J., Hanson, L. Å. Lincoln, K. Ørskov I., Ørskov F & Winberg, J., Studies of urinary tract infections in infancy and childhood. IV Relation of the coli antibody titre to clinical picture and to serological type of the infecting *Escherichia Coli* in acute uncomplicated urinary tract infections. *Acta Paediat Scand* 54 47 1965
3. Andersen, H J Jacobsson B Larson, H & Winberg, J Hypertension, asymmetric renal parenchymal defect, sterile urine and high *E. coli* antibody titre. *Brit Med J* 3 14 1973.
4. Asscher A. W M Lachlan, M. S. F Jones, R. V., Meller S. Sussman, M & Harrison, S., Screening for asymptomatic urinary-tract infection in schoolgirls. *Lancet II*, 1 1973
5. Bergström, T Sex differences in childhood urinary tract infection *Arch Dis Childh*, 47 227 1972.
6. — *A prospective study of urinary tract infection in infancy and childhood*. Thesis, Göteborg 1972.
7. Bergström, T., Jacobsson, B Larsson, H. Lincoln, K. & Winberg, J Symptomatic urinary tract infection in boys in the first year of lif with special reference to scar formation. *Infection*, *1* 192, 1973.
8. Bergström, T Larson, H., Lincoln, K. & Winberg, J Studies of urinary tract infections in infancy and childhood. XII. Eighty consecutive patients with neonatal infection. *J Pediat* 80 858 1972.
9. Bergström T Lincoln, K. Redin, B & Winberg, J Studies of rinary tract infections in infancy and childhood. X Short or long-term treatment in girls with first or second-time urinary tract infections uncomplicated by obstructive urological abnormalities *Acta Paediat Scand* 57 186, 1968.
10. Bergström, T Lincoln, K. Ørskov F Ørskov I & Winberg, J. Studies of urinary tract infections in infancy and childhood. VIII Reinfection vs. relapse. *J Pediat*, 71 13, 1967
11. Campbell, M F Anomalies of the kidney *I* Campbell M. F (ed.) *Urology* W B Saunders Co Philadelphia and London 1963 p 1575
12. Egli, F & Stalder [illegible] Malformations of kidney and rinary tract in chromosomal aberrations I Clinical studies *H maengenetik*, 18 1 1973
13. Ericsson, N [illegible] & Ivemark, B I Renal dysplasia and pyelonephritis in infants and children Part I *Arch Path* 66 255 1958
14. — Renal dysplasia and pyelonephritis in infants and children Part II Primitive ductules and abnormal glomeruli *Arch Path* 66 264 1958
15. Fairley [illegible] F & Butler H Sterile pyuria as manifestation of occult bacterial pyelonephritis with special reference to intermittent bacteriuria. *I* P Kincaid Smith & K F Fairley (eds) *Renal infection and renal scarring* Mercedes, Melbourne 1971 p 51
16. Forbes, P A. Drummond, K. N & Nogrady M. B., Initial urinary tract infections. *J Pediat* [illegible] 187 1969
17. Freedman, L. R. Experimental pyelonephritis. 12. Changes mimicking chronic pyelonephritis as consequence of renal vascular occlusion in the rat. *Yale J Biol Med*, 39 113 1966.
18. — Chronic pyelonephritis at autopsy *Ann Intern Med*, 66. 697 1967
19. Govan, D E. & Palmer J M., Urinary tract infection in children. The influence of successful antireflux operations on morbidity from infection. *Pediatrics* 44 677 1969
20. Hanson, L. Å., Host-parasite relationships in urinary tract infections. Editorial *J Infect Dis*, 127 726, 1973
21. Hepinstall, R., *Pathology of the kidney* Little Brown and Co., Boston 1966.
22. Hermansson, G., Bollgren, L, Bergström, T & Winberg, J Coagulase negative staphylococci as cause of symptomatic urinary infections in children. *J Pediat* 84 807 1974
23. Hodson, C. J Drewe J A. Karn, M. N & King, A., Renal size in normal children. A radiographic study during life. *Arch Dis Childh*, 37 616, 1962.
24. Hodson, C. J & Wilson, S Natural history of chronic pyelonephritic scarring. *Brit Med J* 2 191 1965
25. Jacobsson [illegible] Bergström, T & Winberg, J Renal scarring following nonobstructed infections. To be published.
26. Kass, E. H., Asymptomatic infection of the urinary tract. *Trans Ass Amer Physicians* 69 56, 1956.
27. Kjellberg, S. R., Ericsson, N O & Rudhe, U., *The lower urinary tract in childhood* Almqvist & Wiksell Uppsala 1957 p 172.
28. Kleeman, S E. T & Freedman, L. R., The finding of chronic pyelonephritis in males and females at autopsy *New Eng J Med* 263 988 1960.
29. Kunin, C. M. Pattern of recurrent urinary tract infections in girls. In *Symposium on Pyelonephritis* Livingstone Edinburgh 1966, p 1
30. — *Detection, Prevention and Management of Urinary Tract Infection*. Lee and Febiger Philadelphia 1972.
31. Kunin, C. M Deutscher R. & Paquin, A. Urinary tract infection in school children. an epidemiologic, clinical and laboratory study *Medicine* 43 91 1964
32. Larsson, T Interpretation of mortality and morbidity data. In *Early Phases of Coronary Heart Disease* Skandia International Symposia. Nordiska Bokhandelns Förlag, Stockholm 1973
33. Lincoln, K., *Bakteriologiska studier av primär och recidiverande icke-obstruktiv urinvägsinfektion hos barn* Thesis, Göteborg 1973
34. Lincoln, K. & Winberg, J Studies of urinary tract infections in infancy and childhood II Quantitative estimation of bacteriuria in unselected neonates with special reference to the occurrence of asymptomatic infections *Acta Paediat Scand*, 53 307 1964
35. Lindblad B. S. & Ekengren K The long term prognosis of non-obstructive urinary tract infection in in-

fancy and childhood after the advent of sulphonamides. Acta Paediat Scand 58 .5 1969
36 MacGregor M Pyelonephritis lenta. Consideration of childhood urinary infection as a forerunner of renal in ufficiency in later life Arch Dis Childh 45 159 1970
37 McCabe W & Jackson G Treatment of pyelonephritis. Bacterial drug and host factors in success or failure among 252 patients. New Eng J Med 272 1037 1965
38 Meadow S. R. White R. H R. & Johnston, N M Prevalence of symptomless urinary tract disease in Birmingham schoolchildren. I Pyuria and bacteriuria. Brit Med J 3 81 1969
39 Meares, E. M & Stamey T A Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest Urol 5 492, 1968
40 Mond N C., Grüneberg R. N & Smellie J M., Study of childhood urinary tract infection in general practice Brit Med J 1 602, 1970
41 O'Grady F & Cattell, W R., Kinetics of urinary tract infection I Upper urinary tract. Brit J Urol, 38 149 1966.
42 — Kinetics of urinary tract infection II The bladder Brit J Urol 38 156, 1966.
43 Öfing S. Hanson, L. Å. Holmgren, J Jodal U Lincoln K. & Lindberg, U., The bactericidal effect of normal human serum on E. coli strains from normals and from patients with urinary tract infections. Infection, 1 4 1973
44 Savage D C L. Urinary tract infection in childhood. Scot M d J 16 263 1971
45 Savage D C. L. Wilson M I Ross E. M. & Fee W H A ymptomatic bacteriuria in girl entrant to Dundee primary schools. Brit Med J III, 75 1969
Smallpeice V Urinary tract infection in childhood and its relevance to di ease in adult lif Heinemann Medical Books, London 1968
47 Smellie J M Medical aspect of urinary infection in children J Roy Coll Physician of London 1 189 1967
48 Stamey T A Timothy M Millar M & Mihara G Recurrent urinary infections in adult women. The role of introital enterobacteria Calif M d 115 1 1971
49 Stamey T A Govan D E. & Palmer J M., The localization and treatment of urinary tract infections. the role of bactericidal urine levels as opposed to serum levels. Medicine (Baltimore), 44 1 1965
50 Stansf ld, J M Relapses of urinary-tract infections in children Brit Med J 1 635 1966.
51 — Clinical observations relating to incidence and aetiology of urinary tract infections in children Brit Med J 1 631 1966.
52 Williams D I Paedi tric rology Butterworths, London 1968 p 196.
53 Winberg, J et al Round table conference on nonobstructive urinary tract infections in children. Acta Pediat Scand Suppl 177 42 1967
54 Winberg, J., Andersen, H J Hanson, L. Å. & Lincoln, K. Studies of Urinary tract infections in infancy and childhood I Antibody response in different type of rinary tract infections caused by coliform bacteria. Brit Med J II 524 1963
55 Winberg, J Bergström T Lincoln K. & Lidin-Janson, G., Treatment trial in urinary tract infection (UTI) with special reference to the effect of antimicrobials on the fecal and periurethral flora Cl Nephrol 1 142 1973.
56 Winberg, J Bergström T & Hanson L. Å Neue Gesichtpunkte zur Harnwegsinfektion mit E. coli Msch Kinderheilk 119 306, 1971
57 Winberg, J., Larson H & Bergström T., Comparison of the natural history of urinary infection in children with and without vesico-ureteric reflux I P Kincaid-Smith and K Fairley (eds.): Renal inf ction and renal scarring Mercedes, Melbourne 1971 p 293

More detailed references are found in th earlier papers by this group of authors.

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Key words Pyelonephritis urinary tract infection, epidemiology incidence etiology symptomatology renal scarring

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192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. 1969
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201. Sutherland, Lynette E., Hartroft, Phyllis, Balis, John U., Bailey, John D., and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. 1970
202. Fomon, Samuel J., Filer Jr., L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. 1970
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205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. 1970
206. *Proceedings of the Eleventh Scandinavian Paediatric Congress*, Turku, August 2–August 5, 1970. Edited by Matti Dahl. 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. 1970
209. Rune, Valdemar: Acute Head Injuries in Children. An Epidemiologic, Child Psychiatric and Electroencephalographic Study on Primary School Children in Umeå. 1970
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213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. 1971
214. Samuelson, Göran, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. 1971
215. [illegible], Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped Children. 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. 1971
217. *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposium*. Stockholm, August 30–September 1, 1970. Edited by Claes Thorén. 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. 1971
219. Jaffé, Doris, Hartroft, Stanley, Manning, Mary and Eleta, Graciela, Coronary Arteries in Newborn Children. Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. 1971
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222. Jukarainen, Erkki, Plasma Magnesium Levels during the First Five Days of Life. 1971
223. Fomon, Samuel J., Thomas, Lora N., Filer, Jr. L. J., Ziegler, Ekhard E., and Leonard, Michael T. Food Consumption and Growth of Normal Infants Fed Milk-based Formulas. 1971
224. Klackenberg, Gunnar: A Prospective Longitudinal Study of Children. Data on Psychic Health and Development up to 8 Years of Age. 1971
225. Suoninen, Pirkko, Physical Growth of Children with Congenital Heart Disease. Pre- and Postoperative Study of 355 Cases. 1971
226. Hagberg, Bengt, Sanner, Gunnar, and Steen, Monica, The Dysequilibrium Syndrome in Cerebral Palsy. Clinical Aspects and Treatment. 1972
227. Anttila, Risto, Renal Involvement in Juvenile Rheumatoid Arthritis. A Clinical and Histopathological Study. 1972
228. Hämäläinen, Pentti, Wendelin, Heikki, Riikonen, Osmo, and [illegible], Maria, Chronic Respiratory Paralysis. A Clinical Study of 13 Patients in Long-term Respirator Treatment after Poliomyelitis. 1972
229. Bucci, Giampaolo, Scalamandrè, Antonio, Savignoni, Pier Giorgio, Mendicini, Modesto, Picece-Bucci, Silvana, and with statistical collaboration of Pantanetti, Ludovico, The Systemic Systolic Blood Pressure of Newborns with Low Weight. A Multiple Regression Analysis. 1972
230. [illegible], Ebba, Late Prognosis of Children Born into Tuberculous Households. The Effect of Isolation and Simultaneous BCG-vaccination. 1972
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233. Wendelin, Heikki, Microangiography of the Liver. An Experimental Study of Sheep from the Prenatal to the Postnatal Period. 1973
234. Gerrard, J. W., MacKenzie, J. W. A., Goluboff, N., Garson, J. Z., and Maningas, C. S., Cow's Milk Allergy: Prevalence and Manifestations in an Unselected Series of Newborns. 1973
235. Köhler, Lennart, Health Control of Four-Year-Old Children. An Epidemiological Study of Child Health. 1973
236. *Proceedings of the Seventeenth Nordic Paediatric Congress*, Reykjavik, June 27–June 30, 1972. Edited by [illegible]. 1973
237. Sillanpää, Matti, Medico-Social Prognosis of Children with Epilepsy. Epidemiological Study and Analysis of 245 Patients. 1973
238. Silwer, Jørgen, von Willebrand's Disease in Sweden. 1973
239. Forsius, Harriet, The Finnish Skolt Lapp Children. A Child Psychiatric Study. 1973
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241. Salmi, Toivo T. Haptoglobin Levels in the Plasma of Newborn Infants, with Special Reference to Infections. 1973
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250. Kero, Pentti, Heart Rate Variation in Infants with the Respiratory Distress Syndrome. 1974
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252. Winberg, J., Andersen, H. J., Bergström, T., Jacobsson, B., Larson, H. and Lincoln, K., Epidemiology of Symptomatic Urinary Tract Infection in Childhood. 1974

Printed in Sweden by Almqvist & Wiksell, Uppsala 1974

ACTA PÆDIATRICA SCANDINAVICA SUPPLEMENT 253 1974

RENAL CONTROL OF SODIUM HOMEOSTASIS IN INFANCY

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RENAL CONTROL OF SODIUM HOMEOSTASIS IN INFANCY

by

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STOCKHOLM 1974

Salt is the spice of life?

This survey is based on the following communications

I. Aperia, A., Broberger O., Thodenius, K. and Zetterström, R. Renal response to an oral sodium load in newborn full term infants.
Acta Paediatr Scand 61: 670—676, 1972.

II Aperia, A., Broberger O., Thodenius, K. and Zetterström, R. Developmental study of the renal response to an oral salt load in preterm infants.
Acta Paediatr Scand 63 517—524 1974

III Aperia, A., Broberger O., Thodenius, K. and Zetterström, R. Development of the renal control of salt and fluid homeostasis during the first year of life.
Acta Paediatr Scand In press.

IV Aperia, A., Bergqvist, G Broberger O Thodenius, K. and Zetterström, R.
Renal function in newborn infants with high hematocrit values before and after isovolemic haemodilution.
Acta Paediatr Scand 63 878—884 1974

V Aperia, A., Broberger O Thodenius, K. and Zetterström, R. Renal control of sodium and fluid balance in newborn infants during intravenous maintenance therapy
Acta Paediatr Scand. In press.

These communications will be referred to as I—V

CONTENTS

INTRODUCTION

The sodium intake of adult men has been calculated to be about 2.5 mEq/kg and day Human breast milk has a very low sodium content of about 7 mEq/l, which gives an infant a daily sodium intake of 1.2 mEq Na^+ /kg (60) Does human breast milk have such a low sodium content because the kidney of the newborn infant cannot handle a larger amount or is a low urinary sodium excretion due to the low sodium intake?

Renal function in the newborn mammal has been the subject of many reports in the last decades. Several experimental studies have been performed in young animals of different species as well as in human infants. It is well known that renal function is low (22) as regards glomerular filtration rate (10, 11 48, 69 72), concentrating capacity (23 51 73) and urinary water excretion (2, 12 28 43) At the time this investigation was started, however no studies had been done on the renal control of sodium homeostasis in the immediate neonatal period except for those by McCance et al. in the fifties mainly on piglets (42) Moreover none had been performed in healthy newborn infants of different gestational ages and during the same standardized situations.

In the neonatal period it is possible to evaulate different factors that may be responsible for the control of renal function and to determine how changes in development may influence the homeostatic mechanisms of the kidney Such physiologic data may extend our knowledge of the newborn infant and the ability of the kidney to respond to different demands. This is of importance in the care of very preterm infants, in the treatment of dehydration, and for purposes of ordinary feeding.

The main purpose of this investigation was to determine how the kidney of healthy human infants and of infants with various clinical disorders developed the ability to control sodium homeostasis. The aim has also been to compare the control of sodium homeostasis to the glomerular filtration rate (GFR) and to see how changes in intrarenal physical factors during development influence renal function. The study has therefore included infants of different gestational age and of different postnatal age and with various pathological conditions, such as polycythemia and intravenous saline therapy

MATERIAL

General consideration Since the main aim of this study was to demonstrate the development of sodium homeostasis in the neonatal period in healthy infants, most infants were studied in a maternity hospital or in the preterm ward, where healthy immature infants are admitted. In order not to disturb the mother and child relationship or the start of breast feeding only infants who were not to be breast fed or were admitted to the neonatal ward for other reasons were included. The latter infants were under observation for some minor illness without symptoms of renal disease or malabsorption disorders. All infants were considered to be healthy at the time of the study Before the study no infants had had an abnormal salt intake or an electrolyte disturbance. The findings in these infants are reported in studies I II and III

In studies IV and V the infants were admitted to the neonatal ward or the children s hospital for some more definite clinical disorder In study IV the infants were observed for an abnormally high hematocrit without any other symptoms of illness or renal disease In study V the infants were admitted to the children s hospital for various clinical disorders which are described in more detail in the original paper All of the latter infants were on intravenous fluid maintenance therapy for some clinical reason before the study was started.

Number of infants studied A total of 149 infants were studied. Of these 65 infants were preterm. The number of infants in each study is shown in Table I In this survey the results of findings in 5 full term neonates will also be reported. They were studied in the same way as infants in study I but another method was used for calculating sodium administration. Data are also included on two studies in progress assessing 1) sodium balance in 10 healthy full-term and 28 preterm neonates on routine oral feeding and 2) oral sodium bicarbonate load in 12 full term neonates.

Table I *Number of infants in each study*

	Full-term	Preterm
I	31	—
II	3	44
III	23	—
IV	[illegible]	2
V	19	19

The gestational age of the infants ranged from 28—42 weeks. It was determined both by calculating the days from the first day of the mother s last menstrual period to the day of birth and by physical examination for maturity as judged by neurological examination and external features (3 67) Each infant accepted for the study was appropriate in weight and length for gestational age (24)

Postnatal age In study I the infants were studied from 1—16 days after birth. In study II the infants were studied during the first week after birth, 2—3 weeks after birth and at a time corresponding to expected term, i.e. 40 postmenstrual weeks In study III in which the developmental pattern during the

first year was evaulated, the infants were studied from 3 weeks after birth until 13 months of age. In study IV the infants were studied during the first days after birth. In study V the infants were studied from the first day after birth until 13 days of age. In the study in progress the full-term infants were mostly studied during the first 10 days of life, while the preterm infants were studied during the first months of life.

METHODS

GENERAL CONSIDERATIONS

The infants were disturbed as little as possible. They were not taken from the mother or the ward if they were not in an intensive care unit for clinical reasons before the study started. They were examined in their own cribs or incubators and throughout the study observed by a special nurse who assisted the author in almost all of the investigations.

Urine and blood sampling For ethical reasons bladder catheterizations were not performed in any infant. All urine samples were collected by spontaneous voidings in plastic bags. Each urine sample was collected by a syringe through a tube immediately after voiding. The time between different voidings was calculated in minutes. In order to minimize the amount of blood taken from each infant, capillary blood samples were taken by heel puncture in newborns and by finger prick in older infants. The total amount in each study was generally about 1 ml, and the maximum was about 3 ml.

ADMINISTRATION OF DIFFERENT LOADS

Oral loads of fluid and salt were usually administered by a stomach tube although a feeding bottle was occasionally used in older infants. In study X where intravenous therapy was given, it was always started before the study was performed. The intravenous route, in most instances the umbilical artery or vein, was always chosen by the clinician. In a few patients, however a peripheral vein was used for intravenous therapy For exchange transfusion, study IX the umbilical vein was used. Intravenous infusion, usually into a scalp vein, was also used for a single injection of inulin.

Induction of diuresis Diuresis was induced in all studies, except study X by giving oral fluids — i.e., either breast milk or cow milk formula diluted with water in a proportion of 1:3 in an amount of 2 % of body weight during the first hour and every half hour thereafter in an amount of 0.5 % of body weight for 7—9 hours. No other load, such as oral sodium was given until at least 1½ hours after the start of the induction of diuresis or at least after one urine sample was obtained. Since all studies were performed with a standardized fluid intake, water excretion could also be determined and a comparison made between different infants.

Oral sodium load After induction of diuresis, an oral sodium load of 0.12 g sodium chloride (– mEq Na /kg body weight) was administered during a 30 minute period. The

dissolved to form a 1 %

y diluted breast milk

Urine samples were

collected for at least 5 hours. In study I 6 infants received double the amount of the usual sodium load i.e. 0.24 g/kg body weight (4 4 mEq Na^+/kg body weight). A few infants were also studied without any salt added to the diluted formula.

Validity of the oral fluid and sodium load The same oral loads have previously been used in older children and adults (4 14). It has been shown to be an easy and reliable method and the values found in the older infants were in agreement with those found in adults. The reabsorption from the intestine is regarded to be nearly complete (19 39 40). Even if it is difficult to compare sodium content in the stools, the sodium content was checked in a few newborn infants before and after the salt load. No increase in fecal sodium content was found. No infants developed diarrhea after the salt load. Two newborn infants (I), who received double the sodium load, vomited as did one 9 month old infant (III) who was given the usual salt load by bottle and nipple. These infants were not included in the studies. In the study in progress, where sodium bicarbonate was given instead of sodium chloride, there was a significant increase in the blood serum bicarbonate values. This may be regarded as a criterion of good reabsorption from the intestine even in the newborn infant. An increase in serum sodium 20 minutes after an oral NaCl administration has also been demonstrated by others (34).

Intravenous sodium administration The sodium balance, i.e. renal loss in comparison to intake, was studied in newborn infants requiring intravenous maintenance fluid and electrolyte therapy for clinical reasons (V). These infants were given 5.5 % glucose in an amount of 60—100 ml/kg/day for 5—8 hours with a slow injector (B Braun — Melsungen) The infusion rate was 3.3—3.6 ml/kg/hour (in preterms and full-terms respectively). The exact amount of fluid and sodium given between two voidings could then be calculated. Three different sodium chloride concentrations were used, i.e. 10 20 and 40 mEq/1000 ml. The potassium content of the solution was 20 mEq/1000 ml in all studies.

Body surface area or body weight as a reference All loads were given per kg body weight, because this has been used to a great extent in clinical practice and also because it was used in a previous study which has served as the basis for this study (4) When an oral salt load was given, unless stated otherwise, all the infants received 0.12 g NaCl/kg body weight. This is the same dosage per kg body weight that has previously been given to older children studied in this laboratory When the dosage is related to body surface, however it generally corresponds to 50—60 mEq Na^+/1.73 m^2 in infants and 95 mEq Na^+/1.73 m^2 in older children. (Thus the statement in study I is incorrect that 0 12 g NaCl/kg corresponds to 95 mEq Na^+/body surface). In study I double the amount of sodium chloride was also given and the infants then actually received 0.24 g NaCl/kg corresponding to 100—120 mEq Na^+/body surface. In this survey is also included results from 5 full-term newborn infants given exactly 95 mEq Na^+/body surface. The results were calculated per kg body weight as well as per 1.73 m^2 body surface area and no real difference was noted. The latter method was therefore used for several reasons. It is the most widely used reference in renal function calculations. It has also been recommended for use in developmental studies on renal function (44) It also permits comparison with published values in other age groups.

reported by other authors using the same and different techniques. As neither the condition of the infant nor the fluid intake were the same a direct comparison cannot be made. In this study the GFR was also used for comparison of different groups in infants and as a parameter for comparison of salt excretion. Every effort was made to perform the studies in as similar a manner as possible using the same fluid intake/kg body weight in order to minimize changes in extracellular volume. Admittedly a high fluid intake causes ECV expansion and this might result in falsely high values for the GFR. An increase in extracellular volume of about 10 % could lead to an increased GFR (15) but the fluid intake in these studies was less than this. Moreover the GFR values obtained in this study were similar to those reported by others during the neonatal period and the first months of life. In older infants of about 1 year of age, however higher values were found which might be due to comparatively higher water reabsorption and also to the method that was used for making the calculations. In study V the GFR was determined by continous inulin infusion without bladder catheterization. The results were lower however than expected. It is uncertain whether this was due to the method or to the condition of the infants, as some of them had a low oxygen tension consequent to the respiratory distress syndrome which has been reported to cause a low GFR (63).

DIURESIS

The very preterm infants had also a high diuretic response after the oral standardized high fluid intake of about 150 ml (calculated as average urinary output per hour and body surface area). No significant difference was found between different groups of neonates. In a few infants a somewhat low diuresis was found during the first days of life possibly because of a lower fluid intake before the study was started. No difficulty was found, however in the ability to respond with a fairly high diuresis. High urinary flow rates in the immediate neonatal period have also been reported by others (35). Moreover no significant increase in the diuresis was noted during the first months of life (III). The diuresis was not as great during the intravenous study as during the oral fluid load and fluid balance was slightly positive (V). In some of the preterm infants the balances were negative and the infants lost more water than they had been given. No increasingly negative balance was noted, however. Fluid balance was also studied in normal healthy preterm and full term infants who were on ordinary feedings and not subjected to special load tests. In these infants the fluid balance was positive. Before hemodilution (IV) diuresis was low (104 ± 54 ml) and increased significantly after hemodilution to about the same values as found in healthy newborn infants (160 ± 35 ml).

DILUTING CAPACITY

During the fluid intake very low osmolality values were found. In preterm infants some low values were observed, i.e. 25—35 mOsm/l. Full term infants also had low values i.e. 35 mOsm/l. The diluting capacity or free water clearence which is also an index of distal tubular sodium reabsorption (5) was supernormal in preterm

[illegible] ± SD ml/hou 173 m)

infants and in newborn full-term infants in the immediate neonatal period (I, II). During the first months of life the diluting capacity was also extremely good. After 5 months of age the diluting capacity seemed to diminish and the pattern was more like that found in older children and adults (III 5).

SERUM SODIUM

Serum sodium did not change before and after the sodium load. The serum sodium values were also unchanged in the infants who received intravenous glucose therapy The serum sodium level in normal full term infants ranged from 135—140 mEq/l. No statistical difference was found between preterm infants (II).

In infants who were given intravenous saline, no difference in serum sodium level could be found between the three different groups of infants receiving the different saline infusions. Serum sodium showed no relation to increasing postmenstrual age. (II)

SERUM PROTEIN

Serum protein was low in all infants in the neonatal period (5—6 g %). In preterm infants of increasing postnatal age serum protein decreased. The lowest values were found at an age that corresponded to expected term (II).

SERUM OSMOLALITY

The average serum osmolality was 285 mOsm /l. No difference was found between preterm and full term infants nor with increasing postnatal age. Serum osmolality showed no change before and after hemodilution.

HEMATOCRIT

No change in hematocrit was noted in any neonates during the first week of life and no difference in hematocrit was found at different gestational ages, average value 60 % (I II) With increasing postnatal age the hematocrit decreased most in the very preterm infants. At expected term — i.e. about 2 months of postnatal age, hematocrit values of about 30 % were found (II). Even in full term infants a decrease in hematocrit occurred during the first weeks. The mean value during the first year was 38 % (III). The lowest values were found at 2—3 months of age (III) Hemodilution (IV) produced a significant decrease in hematocrit from 70 % to 60 %. In infants receiving intravenous maintenance fluid therapy (V) somewhat lower hematocrit values were found, i.e. mean value 54 %.

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(me[illegible] ± 1 SD, ml hour 1.73 m[illegible])

DISCUSSION

The ability of the newborn kidney to excrete a sodium load was first studied in the beginning of the 20th century by Meyer et al. (46) after feeding high saline solutions to full term infants. No further reports appeared until Dean and McCance 1949 (21) compared the effect of intravenous hypertonic saline in infants and adults and McCance and Widdowson 1956 (42) studied the effect of oral feeding of hypertonic saline solutions to pigs and three premature infants. They all found that newborn mammals gained in weight, developed oedema and retained sodium when high saline solutions were administered. On the basis of these findings it was concluded that the newborn kidney was unable to excrete excess amounts of salt.

Since initiation of this investigation, the renal response to intravenous administration of different saline loads has been studied in newborn puppies by Kleinman et al. 1974 (36, 37). Their results are discussed in the section below where different factors influencing renal handling of sodium are presented.

The results of the present investigation confirm the view that renal function is low in infancy even when corrected for body surface area. The renal response to an oral salt load was much lower than expected even when corrected for the low glomerular filtration rate (GFR) (I). During the first year of life the development of renal sodium excretion after an oral salt load did not parallel the development of the GFR (III). However at 1 year of age the values corresponded to those reported in older children (14).

Comparison of natriuresis in full-term and preterm neonates showed higher values in neonates of lower gestational age than in neonates born at term (II). These findings therefore accord with those reported in fetuses of different species (1). A decrease has also been noted with increasing gestational age in fractional sodium excretion (47, 75).

Diluting capacity and water diuresis were studied in addition to urinary sodium excretion and GFR. Diluting capacity was extremely high in the neonatal period and started to decrease at about 5—6 months of age. (I, II, III). The decrease in diluting capacity occurred at about the same time as the increase in concentrating capacity (73). The lowest values in water diuresis when calculated after an oral fluid load were found in some infants during the first days after birth which could be due to a low fluid intake before the study or else water diuresis did not change much during infancy in healthy infants (III). The same values were found in preterm and older infants (II, III). This fairly stable response to a high fluid intake must be due to changes in other homeostatic functions of the kidney.

It is thus apparent that the developmental pattern of the various renal function parameter studied is very heterogenous during the first year of life. None of the homeostatic functions studied i.e. Na^+ excretion, water excretion and diluting capacity, parallel the development of the GFR. As regards urinary sodium excretion, it is determined both by the glomerular filtration rate, as filtered load and by tubular sodium reabsorption. Several factors which could influence these functions change during development. These include anatomical development, changes in hydro-

static and oncotic pressure, extracellular volume, extrarenal factors such as sodium and fluid intake and hormonal activity Some aspects of the influence on the function and development of the different parts of the nephron will now be presented.

The low glomerular filtration rate (GFR) could be due to many factors. The results from the present investigation suggest that an inverse correlation exists between the GFR and hematocrit in infants more than 35—36 weeks of gestation (II III IV) The differences in response during postnatal development of very preterm infants and their lack of a rapidly increasing GFR may be related to the information obtained with microdissection studies in the neonatal period (45 53 54). These studies have been performed on kidneys from different species as well as from still borns, dead fetuses and infants. It has been shown that in the human kidney even small glomeruli seems to be completely developed by the age of 36 weeks gestation. No new nephrons are found after this. This would suggest that the glomerulus at very preterm birth i.e before this time is still incompletely developed and cannot respond as well as the glomerulus "at term" to postnatal changes in intrarenal physical factors. The results of this study in infants born after 36 weeks gestation primarily point to glomerular plasma flow as the increase in GFR occurred with a decrease in hematocrit and viscosity (IV) This has also been found by others in experimental studies (6, 9 27). During postnatal development an increase in hydrostatistic pressure (61 52) and decrease in total protein will also occur (66) factors that also may increase GFR.

The development of urinary sodium excretion as well as of the other homeostatic functions studied did not parallel the development of the GFR. Hence it is not surprising that the development of the rest of the nephron, the tubule and collectin ducts, does not parallel that of the glomerulus. Microdissection studies have shown that the tubular mass is comparatively smaller than the glomerular mass in the neonatal period, than later on in life (25 32, 52). A difference between the different tubular parts also seems to exist.

In the neonatal period the proximal tubule has been thought to be shorter than the rest of the tubule (25 49) The function of the proximal tubule has also been studied with micropuncture technique and electron microscopy in invitro studies (31 33) These have shown that the junctions between the proximal tubular cells are not fully developed nor yet so tight. This might create an easier way for sodium transport. For the moment, however it is not known whether this facilitates excretion or reabsorption of sodium in the immature kidney Immature development might therefore be one explanation why preterm infants have a higher natriuresis than full-term infants. On the other hand, physical factors, such as a high oncotic pressure and a low hydrostatic pressure would enhance sodium reabsorption (8, 17 41 58) both of which exist in the neonate As shown in study I there is an inverse correlation between hematocrit and natriuresis in full-term neonates.

The function of the distal part of the tubule seems to be good in the neonatal period. Diluting capacity is regarded as a function of the distal tubule (5). Both in preterm and full term infants diluting capacity was found to be supernormal and very low osmolality values were found (I II III) Sodium reabsorption in the distal tubule therefore seems to be enhanced. From a study on the renal response of the newborn dog, to a saline load a low natriuresis was reported (37). By blocking the function of the distal tubule in these newborn animals it has been possible to considerably increase natriuresis (36). It was thus shown that the enhanced sodium reabsorption in the distal tubule is responsible for the suppressed response to an intravenous sodium load in newborn puppies. It has also been supposed that sodium reabsorption in the

distal part of the tubule is chloride dependent (56). In a study in progress at this laboratory it was also found that the natriuretic response following an oral sodium load is higher if sodium is given as sodium bicarbonate instead of as sodium chloride. Recent studies of sodium reabsorption in the diluting segments of the ascending loop of Henle and early distal tubule also demonstrate a dependency on urea availability (7 50) With a low urea availability which is most likely low in the neonate (23 33 65) sodium reabsorption should be enhanced.

With increasing postnatal age the diluting capacity seems to decline (III). This occurs at a time when the concentrating capacity increases (23 73) The increasing concentrating capacity which in part is due to influence of antidiuretic hormone might also be related to the development of the collecting ducts (68) An increase in the function of the collecting ducts in addition to an increase in the function of the distal tubule might also explain why water diuresis is a high in preterms as in full terms and does not increase with increasing postnatal age (III).

The influence of hormones on renal function seems to be of minor importance in the healthy infants. High aldosterone values, which should act to retain sodium, have not been reported in normal infants except in the immediate neonatal period (13) The rate of aldosterone secretion has in fact been shown to be low during the first week after birth (71) Recently however high plasma renin levels have been demonstrated in the neonatal period (38). The significance of these high values and the effect on sodium retention are not clear however There is at present no conclusive evidence that a natriuretic hormone exists (74).

In conclusion, the above mentioned mechanisms may explain why infants have an enhanced sodium reabsorption and why preterm/immature neonates have a higher natriuresis than full-terms. As demonstrated in the studies on intravenous administration of sodium (V), the newborn kidney has a very low tolerance to salt because the infants were unable to increase sodium reabsorption even when sodium was depleted.

Clinical considerations In studies I—IV the ability to get rid of excess sodium was evaluated. Urinary sodium excretion was found to be low after an oral salt load and was lowest in newborn polycythemic infants (IV). Since GFR and water excretion are also low in these infants, salt and fluid retention might develop, and thus might be dangerous as these infants have a tendency to develop cardiac failure. When prescribing drugs to these infants the low renal function should also be considered. A high salt intake in the neonatal period may also influence the development of hypertension as suggested by studies in newborn rats (20). The risk of giving to small amounts of sodium should also have to be considered as preterm neonates were found to have a higher natriuresis than full terms and might therefore develop a negative salt balance and hyponatremia more readily (II V). In young infants (III) with acute gastroenteritis and an increased extra renal loss or a decreased intake of water the tendency to both sodium retention and excretion of relatively large amounts of diluted urine, might easily lead to the development of hypernatremic dehydration in the presence of a high sodium intake (64).

In study V the ability to maintain the sodium balance, i.e. the ability to reabsorb sodium, was determined during the infusion of the 10 mEq Na^+/l solution. In these sick infants both full-terms and preterms a progressively negative salt balance developed when 10 mEq Na^+/l, which is about the same as the 7 mEq Na^+/l in breast milk, was given. A difference was found even here between preterm and full term infants as full terms infants could maintain a slightly

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SUMMARY

Renal control of sodium homeostasis was studied in 149 infants with a gestational age of 28—42 weeks and postnatal age from birth to 13 months of age. Fifty-seven were healthy full-term infants and 44 were healthy preterms. The remaining 48 infants (preterms as well as full terms) were studied during the course of specific clinical disorders such as polycythemia or different disturbances requiring intravenous maintenance fluid therapy

The main purpose of the study was to determine the sodium tolerance both as regards the ability to excrete a sodium load and to maintain sodium balance. In most of the studies the renal response to an oral sodium and fluid load was investigated (I—IV) and the ability to excrete excess of sodium and fluid was evaluated. The amount of sodium load was generally 0.12 g NaCl/kg body weight (2.2 mEq Na /kg). Urinary sodium excretion was followed for about 5—6 hours after the load.

Urinary sodium excretion was also studied before and after isovolemic hemodilution (IV) All oral studies were performed while the infants were on a standardized fluid intake which was sufficiently high to ensure water diuresis.

The net urinary sodium excretion is dependent both on the amount of sodium filtered and the amount of sodium reabsorbed. In order to evaluate the first factor the glomerular filtration rate (GFR) was determined in about one half of the infants, usually by the method of giving a single injection of inulin. The ability to maintain sodium and fluid balance was assessed by administering intravenous saline in three different concentrations containing 10, 20 and 40 mEq Na^+/1000 ml 5.5 % glucose (V) The studies lasted for 5—8 hours.

In the immediate neonatal period the renal response to an oral salt load was low When compared to older children, full-term newborn infants had about 10 times lower excretion following the same oral salt and fluid load. In these infants an inverse correlation was found between hematocrit and natriuresis. When the natriuretic response was studied before and after hemodilution in infants with polycythemia an increased natriuresis was found which, however was not significant, and which also was parallelled by a significant increase in glomerular filtration rate. All preterm neonates born before 36 weeks of gestation had a higher natriuretic response following an oral salt load than full-term neonates, but with increasing postnatal age the natriuretic response decreased and at the time of term they had about the same values as full-term newborn infants. In full term infants urinary sodium excretion developed linearly during the first year of life and approached the same values reported in older children at the end of the first year

As expected, the glomerular filtration rate (GFR) was low in newborn infants. The lowest values were found in the very preterm infants. The development in full-term infants during the first year of life revealed an exponential increase of the GFR. The values at about 1 year of age corresponded to those found in older children when related to body surface area. It is obvious that the development of the GFR during the first year of life

did not parallel the development of the natriuretic response to an oral salt load.

The osmolality of the urine was very low and ranged from about 25—35 mOsm/l Such values were found in both preterm and full term neonates and are definitely lower than those in older children Osmolar clearance and free water clearance were calculated. Free water clearance is an index of distal tubular sodium reabsorption and also a measure of diluting capacity Diluting capacity was found to be supernormal both in preterm and full term neonates. The diluting capacity was also high during the first month of life. At about 5—6 months of age diluting capacity decreased to values found in older children. Diuresis after an oral fluid load was fairly stable during the first year of life. No difference was found between preterm and full term infants and average diuresis was about the same during the first weeks after birth as during the rest of the first year

The main result of this investigation is that sodium tolerance is low in the neonatal period both as regards the ability to excrete a sodium load as well as the ability to retain sodium during intravenous administration of saline when sodium is depleted. The poor natriuretic response to the oral load can be explained in part by the lower GFR. Since salt excretion and GFR did not parallel each other tubular factors must also be responsible for the sodium retention. The results clearly demonstrate that Na reabsorption in the diluting segments of the nephron per unit filtered load is enhanced. A hypothetical explanation for this enhancement is given. There is no data available that allows conclusions to be drawn regarding proximal tubular reabsorption. It has been suggested however that the relatively high salt excretion in preterm infants may be due to the fact that the relationship between the reabsorptive surface of the proximal tubule and the filtering surface of the glomerular capillaries is smaller in preterm than in full term infants

Calculation of the urinary sodium excretion during intravenous maintenance therapy showed that natriuresis was fairly high. It should, however be noted that the infants included in the study were not healthy and the result cannot therefore be directly compared to the oral studies. Several of these infants were in poor general condition and may have had a low oxygen tension which, according to some reports might result in an increased natriuresis. Among these infants a difference was also found between preterm and full-term infants as average natriuresis was higher in the preterm group Calculation of the changes in sodium and fluid balance controlled by the kidney showed an inability to retain sodium when low saline infusions were administered. A difference was also found between full term and preterm infants as the latter were unable to maintain a slightly positive balance with the same saline concentration as full terms (i.e. 20 mEq Na /100 ml) and instead developed a progressively negative balance At higher saline concentrations preterm infants tended to maintain a balance though still negative However the fluid balance was fairly well maintained in all groups of infants receiving intravenous therapy

ACKNOWLEDGEMENTS

I am greatly indebted to

Professor Rolf Zetterström who introduced me to neonatology for his great interest and fruitful discussions throughout the study as well as for his valuable advice.

Dr Anita Aperia-Broberger for teaching me how to think in research work and for introducing me into the field of nephrology for unfailing enthusiasm, stimulating discussions and constructive criticism.

Dr Ove Broberger head of the pediatric nephrology laboratory for invaluable support and encouragement throughout the investigations.

Dr Gudmund Bergqvist for stimulating collaboration and discussions.

Nurse Kerstin Granén for very skilful assistance and great enthusiasm during all phases of these studies.

The nursing staff of the Neonatal Wards (Dept. 41), Sabbatsberg Hospital and St Göran's Children's Hospital for their interest and help.

Mrs Lill-Britt Svensson, Mrs Eivor Settergren, Mrs Mona Agrén, and Miss Birgitta Kjellman-Kolt for valuable technical assistance.

Mrs Ann-Christine Eklöf for skilful aid in drawing the figures.

Dr Zoe Walsh for kindly revising the English of this survey.

Miss Margret Rask and Miss Helena Nordin for excellent typing of all manuscripts and for secretarial help.

All my friends and colleagues for encouragement and help in various ways.

The studies were supported by grants from the Swedish Medical Research Council (3644), research funds of the Karolinska Institute, the Semper Fund for Nutritional Research and the Föreningen Mjölkdroppen.

REFERENCES

1 Alexander D. P & Nixon, D A. The foetal kidney Brit Med Bull, 17: 11.., 1961

2. Ames, R. G Urinary water excretion and neurohypophyseal function in full term and premature i fants shortly fter birth. Pediatrics 12 .7.., 1953

3 Amiel Tison, C. Neurologic l ev luation of the mat rity of newborn fants. Arch Di Child 43 89 1968

4 Aperia, A Berg, U & Broberger,O : Control of sodium homeostasis children with recurrent rinary tract infections and reduced glomerula filtra ion rates. Acta Paediat Scand 6.. 695 1971

5 Aperia A., Broberger O. & Feychting, H.: The effect of hypotonic mann tol a d saline load on diluti g capacity in man. Act Phys ol S and 8 145 1970

6 Aperia A Broberger O & Herin, P Matu ational hanges in glomerular perf sion rate nd glomerula f ltr ion ate in lambs. P diatr Re 8 758 1974

7 Aperia, A Broberger O & Snellman, K. Tubula re secretion during rgnain fusion i dogs. To be publ hed.

8 Aperia, A., Broberger O & Soderlund, S. Rela tion h p between renal art ry perf sion pressur nd tubular sodium re bsorption. Am J Physiol 2 0 1975 19 1

9 Aperia A. & Herin, P : Dev lopment of glomerul perfusion r nd nephron filtr tion t in 1 —60 days old m Am J Physiol I press.

1 B rrett H. L. Renal ph siology in f ts nd h ldren 1 Method f r est mation of glomerula f l t in te P oc Soc F p Biol M d 44 654 194

11 Barrett, H L., H re K. McN ma H & H re R M rement of glomerular filt tion t in prem ture inf t Cli Inv 691 1948

12 B rrett, H L., Vesterdal, J M N ma a, H & Lauson, H D Ren l w et m in prem re f J Cli Inv 31 1.69 1952.

13 Br s, J F B y d, F Le A L., A et, I G Kerw nki, A. & M geon C. J Plasm l ost m ent el ery d d ing the ewborn per od J Cli Inv 31 356, 1972

14 Berg, U : Urin elimination of a oral salt d fluid load in health children. A ta P ediatr Scand 6 5..5, 1973

15 Brenner B M., Troy J L., D ugharty T M Deen W M. & Robertson C. R. Dy amic of glomerula ultrafiltration in the rat. Plasma flow dependence of GFR. Am J Physiol 23 1184 197

16. Broberger U : Determination of glomerula filtra tion rate in the newborn. Acta P diatr Scand 62 625 1973

17 Burke T J Robinson, R. R. & Clapp J R.: Effect of rterial hematocrit on sodium reabsorption by the pro imal tubu Am J Physiol 2 1 1536, 1971

18 Cl kson, J C. & Smith, K. P M surement f glomerular filtration a in neona es using the single injection cle ran e of 113m In DTPA. A tr P diat J 9 195 1973

19 Cran R. K A perspect of digest e-absorpti function Am J Cli N tr 242, 1969

20. D hl, L. K Heine M & T nan, L.: Effect f hronic ex ss salt i gestion F iden that genetic f ctors plas importa t role sceptibilit to experimental hypertension. J E p Med 115 1173 196..

1 Dean, R. F A. & McCance R. A. The renal responses of inf ts and ad lts to the dmin tration f hypertonic solution of sod. m hl ride d urea. J Ph l (London) 109 81 1949

2 Edelma C. M., J & Spit er A. Th mat rim kidney A modern ew of w ll-b lanced inf t with imbalan ed nephrons. J Pediat 75 5 5 1969

3 Ed lmann C. M J B rrett, H. L. & Troupkou, V Ren l concen ing mech m ewborn infan s. Effect of dietary protei nd w ter on tent, rol f a d respon eness t d e tic hormone J Cli I t 39 1 6.. 196..

4 F nt om, L., Ka llberg, P & Sel tam U N onatal Li gd kt J Håll and ull g and tistd 19 1 Copyright.

25 Fet erman, C. F Shuplock, N A., Ph l pp F J & Gregg, H S The growth and ma at n of h ma g merula d proximal con l t le from ter ad l hood. P diatric 35 6 1 1965

26. Fomon, S. J. *I fant nutrition*. W B. Saunders, Philadelphia and London. P 162, 1967
27 Gruskin, A. B., Edelmann, C. M., Jr & Yuan, S. Maturational changes in renal blood flow in piglets. *Pediatr Res*, 4 13 1970.
28. Heller H. The water metabolism of newborn infants and animals. *Arch Dis Child*, 26 195 1951.
29 Heyrovsky A. A new method for the determination of inulin in plasma and urine. *Clin Chim Acta*, 1 470, 1956.
30. Hilger H. H., Klumper J D & Ullrich, K. J Wasserrückresorption und Ionentransport durch die Sammelrohrzellen der Säugetierniere *Arch ges Physiol*, 267 218, 1958.
31 Horster M. Glomerular — tubular balance — total kidney and single nephron in the developing kidney Third Int Symp of Ped Nephr Washington, 1974
32 Horster M Kemler B. J & Valtin, H. Intracortical distribution f number and volume of glomeruli during postnatal maturation in the dog *J Clin Invest* 50 796, 1971
33 Horster M. & Valtin, H. Postnatal development of renal function Micropuncture and clearance studies in the dog. *J Clin Invest* 50 779 1971
34 Janovský M., Martínek, V & Stanncová, V Antidiuretic activity in plasma of human infants after load of sodium chloride. *Acta Paediatr Scand* 54 543, 1965
35 Jones, M.D J Gresham, E.L. & Battaglia, F C. Urinary flow rates and urea excretion rates in newborn infants. *Biol Neonate* 21 321 1972.
36. Kleinman, L. I. Renal sodium reabsorption during saline and distal blockade in newborn dogs. *Am J Physiol*. In press.
37 Kleinman, L. I. & Reuter J H. Renal response of the newborn dog to saline load The role of intrarenal blood flow distribution. *J Physiol*, 239 225, 1974
38. Kotchen, T A., Strickland, A. L., Rice, T W & Walters, D R. A study of the renin-angiotensin system in newborn infants. *J Pediatr* 80 938 1972
39 Kramer P Kearney M. P & Ingelfinger F J The effect of specific foods and w ter loading on the ileal excreta of ileostomized human subjects. *Gastroenterology* 42 535, 1962.
40. Levitan, R Colonic absorption of electrolytes and water *Am J Clin Invest* 22 315 1969
41 Lewy J E & Windhager E. E Peritubular control of proximal tubula fluid reabsorption i the rat kidney *Am J Physiol*, 214 943 1968.
42. McCance, R A & Widdowson, E. M Hypertonic expansion of the extracellular fluids. *Acta Paediatr Scand* 46 237 1957
43. McCance, R. A. & Young, W F F: The secretion of urine by newborn infants. *J Physiol* 99: 265, 1941
44 McCrory W W.: *Developmental Nephrology* p. 93—108, Harvard University Cambridge, Massachusetts, USA, 1972.
45. McDonald, M. S. & Emery J L. The late intrauterine and postnatal development of human renal glomeruli. *J Anat (London)*, 93 331 1959
46. Meyer L. F & Cohn S. Beobachtungen und Stoffwechselversuche über die Wirkung verschiedene Salze beim Säugling. *Z Kinderheilk* 2: 360, 1911
47 Moore E. S., Galvez, M. B., Paton, J. B., de Lannoy C. W & Ocampo, M.: Third Int Symp of Ped Nephr Washington, USA, 1974
48. Oh, W Oh, M. A.& Lind, J Renal function and blood volume in newborn infants related to placental transfusion. *Acta Paediatr Scand* 56: 197 1966.
49 Osathanondh, V & Potter E. L. Development of human kidney as shown by microdissection. IV Developmen of tubular portions of nephrons. *Arch Path* 82 391 1966.
50. Pennell, J P Lacy F B. & Jamison, R. L.: An in vivo study of the concentrating process in the descending limb f Henle' loop *Kidney I* : 5 337 1974
51 Poláček, E., Vocel, J Neugebauerová, L., Sebková, N. & Věchetová, E. The osmotic concentrating ability in healthy infants and children. *Arch Dis Child* 40 291 1965
52. Potter D Jarrah, A., ..., T Harrah, J & Holliday M. A. Character of function and size in kidney during normal growth of rats. *Pediatr Res*, 3 51 1969
53 Potter E. L.: Development f the human glomerulus. *Arch Path*, 8? 241, 1965
54 Potter E. L. & Thierstein, S. T Glomerular development in the kidney as a index of fetal maturity *J Pediatr* 22 695 1942.
55 Rand, P W Lacombe, E., Hunt, H. E. & Austin W H.: Viscosity of normal human blood under normothermic and hypothermic conditions. *J Appl Physiol*, 19 117,1964
56. Rocha, A. S & Kokko, J P Sodium ch... and water transport in the medullary thick ascending limb of Henle Evidence for active ...ride transport. *J Clin Invest* 52 61... 1
57 Sapirstein, L. A., Vidt, D G Mandel ... Hanusek, G. Volumes of distribution ... ces of intravenously injected creatinine *Am J Physiol*, 181 330, 1955
58. Schrier R. W & Earley L. E. F... crit on renal hemodynamics and ...

in hydropenic and plasma expanded dogs. *J Clin Invest* 49:1636, 1970.

59. Silkalns, G I, Jeck, D, Earon, J, Edelmann, C M, Jr, Chervu, L R, Blaufox, M D & Spitzer, A: Simultaneous measurement of glomerular filtration rate and renal plasma flow using plasma disappearance curves. *J Pediatr* 83 749 1973

60. Socialstyrelsen medicinska expertgrupp för kost och fysisk aktivitet i barnaåldern 0—18 år (MFK B). (Report from National Board of Health and Welfare: Diet and physical activity in children). *Socialstyrelsen redovisar* nr 33 1973

61. Spitzer A. & Brandis, M. Functional and morphologic maturation of the superficial nephrons. Relationship to total kidney function. *J Clin Invest* 53 279 1974

62. Spitzer A. & Edelmann, C. M. Jr: Maturation changes in pressure gradients of glomerular filtration. *Am J Physiol* 221:1431 1971

63. Svenningsen, N. W.: Single injection polyfructosan clearance in normal and asphyxiated neonates. *Acta Paediatr Scand* 1974 In press.

64. Taitz L. S.: Overfeeding in infancy. *Proc Nutr Soc* 33 113 1974

65. Trimble M. E.: Renal response to solute loading in infant rats. Relation to anatomical development. *Am J Physiol* 219 1089 1970.

66. Tudvad, F. Birch-Andersen, A. & Blamer, I.: Serum protein values in premature infants: Paper electrophoresis. *Acta Paediatr Scand* 46:329 1957

67. Usher R., McLean, F. & Scott, K. Judgement of fetal age II. Clinical significance of gestational age and an objective method for its assessment. *Pediatr Clin N Amer* 13 835 1966.

68. Vesterdal, J: The endocrine control of the water balance in the newborn. *Biol Neonat* 1 44 1966.

69. Vesterdal J & Tudvad, F.: Studies on the kidney function in premature and full term infants by estimation of inulin and paraamino hippurate clearance. *Acta Paed* *Scand* 37 429 1949

70. Vögeli, B. Riedwyl, H., Donath, A. & Oetliker O.: Comparison of glomerular filtration rate and effective plasma flow determinations obtained by a single injection technique and by means of a standard clearance technique in children. *Acta Paediatr Scand* 63 S.8 1971

71. Weldon, V. V. Kowarski, A. & Migeon, C. J.: Aldosterone secretion rates in normal subjects from infancy to adulthood. *Pediatrics* 39 713 1967

72. West, J. R., Smith, H. W. & Chasis H.: Glomerular filtration rate, effective renal blood flow and tubular excretory capacity in infancy. *J Pediatr* 32:10, 1948.

73. Winberg, J. Determination of renal concentrating capacity in infants and children without renal disease. *Acta Paediatr Scand* 48:318 1959

74. Wright, F. S. Brenner B. M., Bennett, C. M., Keimowitz R. I., Berlinger R. W. Schrier R. W. Verroust, P. J. de Wardener H. E. & Holzgreve H. Failure to demonstrate a hormonal inhibitor of proximal sodium reabsorption. *J Clin Invest* 48 1107 1969

75. Zetterström, P. M. & Houston I. B.: Intrauterine renal function and the amniotic fluid. Third Int Symp of Ped Neph Washington, USA, 1974

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229. Bassi, Giovanni, Zambonardo, Antonio, Borgogni, Pier Giorgio, Mandelsted, Nicholas, Ponce-Barsi, Silvano, and with statistical collaboration of Fiamanes, Ludovico, The Systemic Systolic Blood Pressure of Newborns with Low Weight. A Multiple Regression Analysis. 1972
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Cover printed in Sweden by Almqvist & Wiksell, Uppsala 1975

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ACTA - / SUPPLEMENT 254 1975
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INDICATOR DILUTION STUDIES BY EARPIECE DENSITOMETRY IN INFANTS AND CHILDREN WITH CARDIOVASCULAR DISEASE

EDITED BY C. GÖRAN WALLGREN

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From the Cardiovascular Laboratory Department of Pediatrics,
Karolinska Hospital Stockholm.

INDICATOR DILUTION STUDIES BY EARPIECE DENSITOMETRY IN INFANTS AND CHILDREN WITH CARDIOVASCULAR DISEASE

a collection of articles
edited by

C. GÖRAN WALLGREN M.D

STOCKHOLM 1975

I VALIDITY OF DICHROMATIC EARPIECE DENSITOMETRY FOR QUANTITATIVE STUDIES IN CHILDREN WITH SHUNT FREE CARDIOVASCULAR MALFORMATIONS

by

C. GÖRAN WALLGREN, JOHN S. HANSON,
GÜNTER KRETZSCHMAR and PER ZETTERQVIST

ABSTRACT Cardiac output was assessed in 16 children without evidence of cardiovascular shunts from simultaneously recorded earpiece and cuvette densitometric tracings. The earpiece set-up was calibrated by the end-tail method. Both instruments gave linear response to dye concentrations used. There was a close correlation between cardiac output figures recorded by the two methods (r=0.95) and no systematic difference occurred.
It is concluded that in infants and children earpiece densitometry constitutes a rapid and accurate method for quantitative circulatory studies.

KEY WORDS Earpiece densitometry cardiac output.

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The functional appraisal of the circulatory system in congenital heart disease ideally requires the identification and quantitation of shunt flow as well as the assessment of resistance to blood flow in specific parts of the circulation. Whereas the magnitude of a shunt usually is determined by semiquantitative methods based on A-V O_2 difference estimates the calculation of cardiac output is needed for the evaluation of vascular resistance. To satisfy the Fick equation for cardiac output determination the oxygen consumption must be known and necessitates the collection of expired air. This is usually a tedious undertaking in younger children and infants who do not readily accept the various collecting equipment. Although techniques have been suggested to facilitate the quantitation of oxygen consumption (23) most laboratories seem to consider the Fick method too cumbersome for use in infants and children and usually rely on relative figures for flow and resistance or cardiac output estimates from "predicted" oxygen consumption values (11).

The shortcomings of these measurements are evident and values thus obtained incorporate errors due to lack of basal state during catheterization in small children. Whereas these assessments may be of value for the clinical evaluation of the cardiovascular situation at hand their low reliability preclude their use in most scientific contexts

With this dilemma in mind a search for a method capable of determining cardiac output and shunt flow in small children was initiated The method ought to be safe, sensitive and applicable without procedures likely to arouse the patient.

Indicator dilution techniques have long been an alternative to the Fick method for cardiac output determinations in man. Two different techniques have found wide application thermal dilution and dye dilution. Whereas the

former seems ideally suited for the evaluation of perfusion in a given vessel, its limitation with respect to shunt evaluation reduces its overall diagnostic value in congenital heart disease. Dye dilution technique was accordingly considered the method of choice. In order to make the technique more easily applicable to small subjects, however, arterial sampling had to be avoided. The following investigation was undertaken to evaluate the validity of the "external" earpiece densitometry for quantitative circulatory studies.

Material and methods. 16 children admitted to the clinic for routine evaluation of congenital heart disease were included in the study. Age at investigation varied between 5 and 16 years (mean 10.5). They were all suffering from various types of stenotic heart lesions or were catheterized postoperatively after successful repair of intracardiac septal defects. Children with signs of intracardiac shunts or valvar regurgitation were excluded from the study. None of the patients was in cardiac failure at the time of the investigation. Cardiac catheterization was performed after routine premedication with standard preparations (17).

Following percutaneous introduction of a venous and arterial catheter a diagnostic catheterization was performed and the catheters were subsequently positioned with the venous tip in the main pulmonary artery and the arterial tip in the aortic arch.

Dye dilution techniques. Earpiece densitometry. Dye dilution with "external" recording was performed with a Waters D 401 dichromatic densitometer with earpiece photometry. The earpiece was attached to the ear after rubbing the pinna for one minute with rubrifacient ointment (Transvasin®) which caused intense reddening of the skin. Care was exercised not to squeeze the pinna between the jaws of the earpiece and the built-in spring was usually not allowed to exert its full tension. To accomplish stable positioning of the unit it was secured to the ear with adhesive tape. The ear was subsequently covered with green cloth to prevent influence of ambient light on the photocell. The densitometer signal was fed to a direct writing recorder with a response time of less than 0.5 sec. for full scale deflection (Honeywell Electronik). The densitometer was calibrated by the end tail method ( ) in the following manner. Three dye free samples of 5 ml each were withdrawn from the patient prior to introduction of dye. Two of these samples were mixed up to 5 and 10 mg/L dye concentration respectively by the administration of dye from the actual dye solution to be used in the patient.

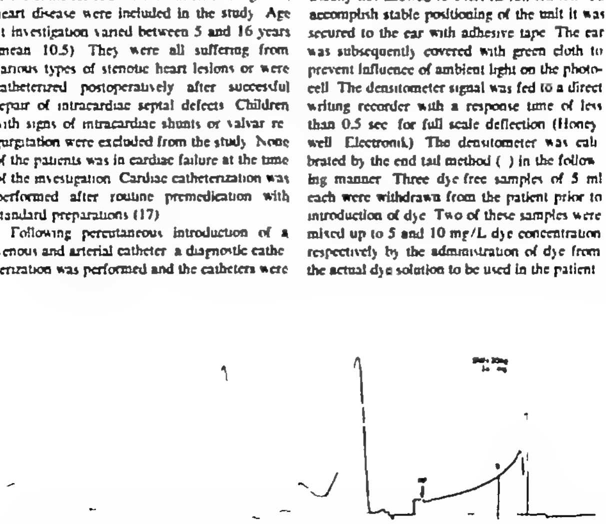

Fig. 1. Dye d[illegible] tracings from [illegible] year old boy with [illegible]. The right half of the figure [illegible] the end tail calibration [illegible] after [illegible] of 4 mg of Cardiogreen. S = [illegible] for calibration. [illegible] catheter [illegible] Chart speed 5 cm/m[illegible]. The left side of the [illegible] dilution curves recorded [illegible] speed of [illegible] reproducibility of the curves. Chart runs right to left.

The third dye-free sample was later used as zero reference. After a 5 minute warm-up period, the baseline of the instrument was checked by letting it run for some minutes with the densitometer in "operate" position. A baseline drift of less than 1 mm/min was achieved in every instance and was considered small enough to be neglected as a source of error. Two mg of dye (Cardiogreen*) per kg. bodyweight was injected through the venous catheter which was immediately flushed forcefully with the patient's blood to ensure that no residual dye was left in the catheter-syringe system. The concentration of dye was continuously recorded and when the decay of dye yielded an exponential curve, which was achieved usually within 2 minutes, a blood sample was withdrawn through the venous catheter and the sampling time noted on the recorder chart (Fig. 1). The dye concentration of the end-tail sample and thus calibration of the instrument, was determined by running this sample together with the zero sample and the 5 and 10 mg/L samples through a modified earpiece-cuvette arrangement according to Barr et al. (1). This calibration technique was found to be simple, rapid and automatically indicative of the instrument linearity.

Cuvette densitometry: Arterial dye curves were recorded simultaneously during the earpiece densitometry by withdrawal of blood from the arterial catheter at a rate of 20 ml/min. The densitometer equipment connected to the arterial catheter was a Waters λ 301 system and the dye dilution curves were recorded on an instrument with response characteristics similar to that of the earpiece equipment. The cuvette was calibrated in series with the earpiece-cuvette assembly.

Experimental procedures: Dye solutions containing 1 mg/ml of Cardiogreen were made up and the venous catheter was filled with dye solution. A bolus of dye was subsequently administered by injecting 1 or 2 ml of solution into the pulmonary artery. With this method an exact amount of dye is "displaced" into the blood stream and no flushing of the catheter is needed. The technique has previously been evaluated in newborn infants and found well suited for quantitative work (21). With the technical set-up just described, dye dilution curves were recorded simultaneously from the aortic arch and the capillary bed of the ear pinna allowing a comparison between the two methods.

As the present case material was made up of patients without shunts or valvar regurgitation, all patients exhibited clean, undisturbed primary dilution curves without interference with cardiac output calculation by recirculation. The rapid area calculation suggested by Bradley and Barr (3) was used and cardiac output determinations were made in three consecutive curves from the two recorders. Corresponding individual observations were compared as well as mean values for the three observations and the data were submitted to standard statistical evaluation.

RESULTS

Linearity: Both earpiece and cuvette showed linearity in their response to dye concentrations in the ranges used for densitometry. The densitometer calibration constant (mg/L/cm) computed from the 5 mg/L standard did not differ in any instance by more than 3 % from that computed from the 10 mg/L standard. There was no systematic change in cardiac output computed from as many as 10 consecutive dilution curves in the same patient indicating that background suppression did not constitute a problem.

Pulse artifact suppression. As a rule, the earpiece recordings were superior to cuvette recordings with respect to flow and pulse artifact suppression. Whereas the pulse contour was hardly recognizable in the earpiece tracings, it was a marked feature in the cuvette curves which often had to be arbitrarily smoothed out for area calculation.

Sensitivity to dye concentration changes. With identical recorder amplification the two methods gave approximately the same deflection for a given dye concentration. Although

former seems ideally suited for the evaluation of perfusion in a given vessel, its limitation with respect to shunt evaluation reduces its overall diagnostic value in congenital heart disease Dye dilution technique was accordingly considered the method of choice In order to make the technique more easily applicable to small subjects, however arterial sampling had to be avoided The following investigation was undertaken to evaluate the validity of the external earpiece densitometry for quantitative circulatory studies.

Material and methods 16 children admitted to the clinic for routine evaluation of congenital heart disease were included in the study Age at investigation varied between 5 and 16 years (mean 10.5) They were all suffering from various types of stenotic heart lesions or were catheterized postoperatively after successful repair of intracardiac septal defects. Children with signs of intracardiac shunts or valvar regurgitation were excluded from the study None of the patients was in cardiac failure at the time of the investigation Cardiac catheterization was performed after routine premedication with standard preparations (17)

Following percutaneous introduction of a venous and arterial catheter a diagnostic catheterization was performed and the catheters were subsequently positioned with the venous tip in the main pulmonary artery and the arterial tip in the aortic arch.

Dye dilution techniques· Earpiece densitometry· Dye dilution with external recording was performed with a Waters D 401 dichromatic densitometer with earpiece photometry The earpiece was attached to the ear after rubbing the pinna for one minute with rubrifacient ointment (Transvasin®) which caused intense reddening of the skin. Care was exercised not to squeeze the pinna between the jaws of the earpiece, and the built-in spring was usually not allowed to exert its full tension. To accomplish stable positioning of the unit it was secured to the ear with adhesive tape The ear was subsequently covered with green cloth to prevent influence of ambient light on the photocell The densitometer signal was fed to a direct writing recorder with a response time of less than 0.5 sec. for full scale deflection (Honeywell, Electronik) The densitometer was calibrated by the end-tail method (2) in the following manner Three dye-free samples of 5 ml each were withdrawn from the patient prior to introduction of dye Two of these samples were mixed up to 5 and 10 mg/L dye concentration respectively by the administration of dye from the actual dye solution to be used in the patient.

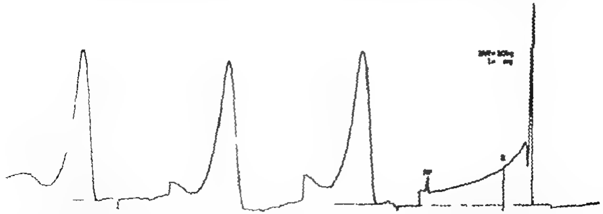

Fig 1 Dye dilution tracings from 7 year old boy with aortic stenosis. The right side of the figure show the end-tail calibration procedure after injection of 4 mg of Cardiogreen. S = sample for calibration. RF = catheter refilled with indicator Chart speed 5 cm/min. The left side of the tracing depicts 3 actual dilution curves recorded at chart speed of 30 cm/m Not the great reproducibility of the curves. Chart runs right to left

tative earpiece densitometry to the pediatric population has, to our knowledge not been reported

Since earpiece densitometry for quantitative use incorporates such methodological shortcomings as the end-tail calibration procedure, it would be of interest to compare our correlation figures with those reported between cuvette observations in the same patient. In order to assess the instrumentation error inherent in the dye dilution technique with cuvette densitometry Hanson and Tabakin (9) compared cardiac output determinations from two sets of arterial cuvette set-ups arranged in tandem with both cuvettes observing the same blood sample. They also performed dilution curves from different parts of the arterial system but recorded simultaneously When the present results are rearranged, to allow comparison with the cited observations our fit between cuvette and earpiece recordings is only slightly inferior to that reported for the tandem cuvette arrangement and somewhat better than that reported when simultaneous cuvette tracings from different arteries are compared. It seems logical to assume that the smoothness of earpiece recordings improves the area calculation and hence would serve to reduce the instrumentation error of the method. This is also in agreement with the findings of a smaller coefficient of variance for repeated observations with the earpiece technique A second factor which may have some bearing on the closer correlation of the earpiece-cuvette plot is the method of area calculation. The fore-n-aft triangle formula of Bradley and Barr (3) employed in the present investigation by necessity incorporates a number of standardized area approximations which may possibly improve the reproducibility of the dye dilution method but consequently add a stabilizing factor to the output determination. It should be noted, however that earlier comparative studies between earpiece and cuvette densitometry in adult man (7) have yielded almost identically high correlation coefficients with conventional area calculation.

It may be argued that infants and small children are not really represented in the present material and that earpiece recordings and quantitation of cardiac output in the younger age groups might yield less accurate results Whereas for technical reasons smaller children had to be excluded in the present investigation, where arterial sampling was deemed difficult or not indicated, quantitative earpiece studies from these infants yielded cardiac output figures in good agreement with cardiac indices recorded in this age-group by oxygen methods (23)

The present method of calibration which uses 20 ml of whole blood, or 10 ml with 1/1 dilution, may be considered less well suited for studies in small infants Micromethods have consequently been devised where the whole blood requirement may be kept below 2—3 ml (10), a volume which ought to be almost negligible with respect to the circulatory homeostasis of the newborn.

In conclusion, it is evident that the "traditional" difficulties associated with earpiece densitometry for quantitative use can be overcome with a certain amount of precaution. Earpiece densitometry seems to be a method well suited for cardiac output determination in children with various types of obstructive cardiovascular malformations. The applicability of the method in the presence of left-right shunt flow will be evaluated in a following communication.

REFERENCES

1 Barr J W and Bradley E. C. A calibration device for the earpiece dichromatic densitometer *J Appl Physiol* 25:633, 1968.

2. Beard, E. F and Wood, E. H Estimation of cardiac output by dye dilution method with ear oximeter *J Appl Physiol*, 4 177 1951

3 Bradley E. C. and Barr J W Fore-n-aft triangle formula for rapid calculation of area. *Amer Heart J* 78:643 1969

4 Bruce, T A. and Shillingford, J P The normal resting cardiac output. Serial determinations by a dye dilution method. *Brit Heart J* 4 69 196..

5 F holt, W and Fabricius, J E aluation of dy injection method in congenital heart disease. *Brit Heart J* 20:117 1958.

6 Fox, I. J Brooker E. C., Heseltine, D W

Essex, H. E. and Wood, E. H. A tricarbocyanine dye for continuous recording of dilution curves in whole blood independent of variation in blood oxygen saturation. *Proc Staff Meet Mayo Clin*, 32:478, 1957
7 Gabe, I T and Shillingford, J P. The photoelectric earpiece technique for recording dye dilution curves. *Brit Heart J* 23:271 1961
8. Gabe, I T Tuckman, J and Shillingford, J P Determination of relative changes in cardiac out put from non calibrated earpiece dye dilution curves. *Circ Res*, 11:405 1962.
9 Hanson, J S and Tabakin, B S. Simultaneous and rapidly repeated cardiac output determinations by dye-dilution method. *J Appl Physiol* 19:275 1964
10. Kretzschmar G W. A micro method for calibration of the dichromatic earpiece. *Act Paediat Scand* t be published.
11 La Farge, C. G and Miettinen, O S. The estimation of oxygen consumption. *Cardiovasc Res*, 4 23, 1970.
12. Phinney A. O Clason, W P Stoughton, P V and McLean, C. E. Measurement of cardiac out put using the photoelectric earpiece: A comparison with simultaneous Fick measurements. *Circ Res* 3:80, 1963
13 Prec, K. J and Cassels, D E. Dye dilution curves and cardiac output in newborn infants. *Circulation*, 11 789 1955.
14 Reed, J H. and Wood, E. H. Use of dichromatic earpiece densitometer for determination of cardiac output. *J Appl Physiol* 23:373, 1967
15 Schneider K. W Cheikhzadeh, A and Müller W Die Bestimmung der Herzminutenvolumens mit einer dichromatischen Ohrdensitometer und vereinfachter Berechnung durch Computer *Cardiolologia*, 51:349 1967
16. Sekelj, P Bates, D. N Johnson, A. L. and Jegier W. Estimation of cardiac output in man by dye dilution method using an automatic computer oximeter *Amer Heart J* 55:810, 1958.
17 Smith, C., Rowe, R. D. and Vlad, P Sedation of children for cardiac catheterization with an tar actic mixture. *Canad Anaesth Soc J* 5:35 1958.
18. Sutterer W F and Wood, E. H. A compensated dichromatic densitometer for indocyanine green. *IRE Trans Bio Med Electron*, 9:133, 1962.
19 Swan, H J and Wood, E. H Localization of cardiac defects by dye dilution curves recorded after injection of T 1824 at multiple sites in the heart and great vessels during cardiac catheterization. *Proc Staff Meet Mayo Clin*, 28:95 1953
20. Swan, H. J Zapata Diaz, J and Wood, E. H. Dye dilution curves in cyanotic congenital heart disease. *Circulation*, 8 70, 1953
21 Wallgren, C. G. Ed. Quantitative Studies of the Human Neonatal Circulation. *Acta Paediat Scand* Suppl. 179, 1967
22. Watanabe, T Kato, K., Watanabe, H. and Koyama, S. Determination of cardiac output by ear piece dye dilution technique at rest and during exercise. *Jap Heart J* 7:36, 1966.
23 Wessel, H., Rorem, D Muster A Acevedo, R. and Paul, M Continuous determination of oxygen uptake in sedated infants and children during cardiac catheterization. *Amer J Cardiol* 24 376 1969
24 Wood, E. H., Swan, H J and Helmholz, H. F Recording and basic patterns of dilution curves Normal and abnormal. *Proc Staff Meet Mayo Clin*, 32:464 1957

II CARDIAC OUTPUT STUDIES IN INFANTS AND CHILDREN UNDERGOING RIGHT HEART CATHETERIZATION

by

C. GÖRAN WALLGREN, GÜNTER KRETZSCHMAR and PER ZETTERQVIST

ABSTRACT Cardiac output figures from 97 patients were computed by earpiece densitometry and correlated to various dimensional parameters. Stroke volume was better correlated to body dimensions than cardiac output indicating that patients undergoing right heart catheterization were not in basal state.

KEY WORDS Earpiece densitometry Cardiac output, Cardiovascular malformations.

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The indicator dilution technique with ear piece recording of the dye curve has been documented as an accurate and easily applicable method for cardiac output determination in infants and children (12) The procedure has been in routine use in our laboratory during the last few years and has been used in patients from the newborn period to adolescence The quantitation in absolute terms of cardiac output has rendered the catheterization data considerably more reliable and enhanced a meaningful interpretation of the cardiovascular situation at hand.

The following investigation reports on data regarding cardiac output, stroke volume and heart rate during routine catheterization of the right heart in infants and children.

Material and methods: 97 patients constitute the subject material, for the present study The age of the patients varied between 48 hours and 20 years with a mean of 9 1 years. The age distribution of the population is depicted in Fig 1 There were 35 girls and 6 boys. These 97 patients constitute a selected population in as much as they did not exhibit any signs of right-left or left-right cardiovascular shunts. Shunt cases were excluded from the present investigation since the presence of cardiovascular shunts might interfere with the area calculation of the primary dye curve and thus invalidate the method for quantitation of cardiac output.

The subject material includes 41 instances of various stenotic leasons such as aortic and pulmonic stenosis and coarctation of the aorta, all of them with significantly increased systolic load of the pertinent ventricle Of the remain-

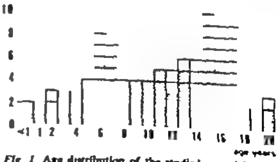

Fig 1 Age distribution of the studied material.

ing 56 cases 33 were postoperative studies including 14 corrected cases of Tetralogy of Fallot and 19 surgically closed ASD and VSD patients. These were all patients with normal or only slightly increased pressure in the right ventricle The remaining 23 patients represented either minor cardiac defects without significant ventricular overload or were found to have entirely normal circulatory systems The 56 patients with normal or essentially normal hemodynamics were treated as one group (grp 1) separate from the 41 patients with systolic overload (grp 2.)

All patients were studied early in the morning with feeding withheld for 12 hours prior to the investigation. There was no instance of cardiac failure in the material and the radiological heart size was within normal limits Newborns and small infants were as a rule studied without any sedation whereas older children were given routine premedication (11) Care was exercised not to perform a dye study during states of arousal and the patients were usually quiet although not basal during the time of the study

The dye curves were recorded with a Waters D 401 dichromatic densitometer with an earpiece photocell and recorded at a paper speed of 0.5 cm/sec. The recorder had a response time of less than 0.5 sec for full scale deflection The earpiece set-up was calibrated by the endtail method and the calibration device suggested by Barr and Bradley (1) which also allows a check of the overall linearity of the instrument assembly A detailed description of the dye injection technique and the calibration procedure is provided elsewhere (12) Injection site was in all instances the main pulmonary artery and the injected amount was either 1 or 2 mg of Cardiagreen depending on the size of the patient. Injection was instantaneous and the injection time marked on the recorder Dye curves were inscribed at the end of the catheterization and were followed by angiocardiography where indicated A minimum of three technically good tracings was obtained from every patient. The rapid area calculation method (2) was used for the assessment of cardiac output. The mean of three output values was taken as representative for the patient under study

In 24 patients who were cooperative enough to allow collection of expired air a Fick analysis was performed in close proximity to the dye study to serve as a rough estimate of the correlation between the two methods for cardiac output determination. Ninety-seven per cent saturation of the arterial blood was assumed and no arterial sampling was performed for calculation of the arteriovenous oxygen difference

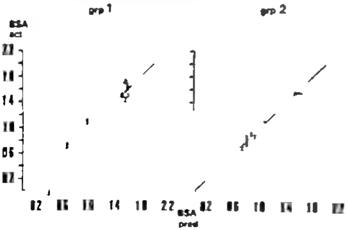

Fig 2 Physical development of th subject material expressed ctual body surface area (BSA act) as related to the expected (BSA pred) from standard height/weight nomograms

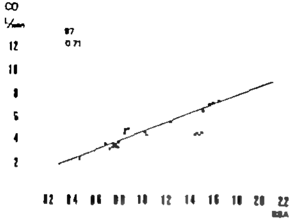

Fig. 3. Cardiac output related to body surface area in both groups of patients (see text). Coefficient of correlation 0.71

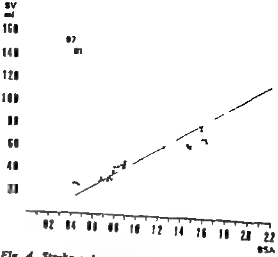

Fig. 4. Stroke volume (SV) related to body surface area. Coefficient of correlation 0.79. Regression line equation SV = 57.9×BSA —8.6.

Results. The physical development of the patients is graphically plotted in Fig. 2 expressed as actual BSA calculated from the DuBois nomogram (6) as compared with the predicted BSA from height and weight standards for the age of the patient (8). Whereas the "normal" group is fairly closely distributed around the line of identity there exists in the "pressure overload group" a number of cases well below the predicted normal BSA value. There were as a rule only minor differences between the three computed cardiac output figures for every patient. Mean coefficient of variance = ± 5.1 %.

Cardiac output was poorly correlated to the body surface (r = 0.71) for the whole material and there was no statistically significant difference in this respect between the groups (Fig 3).

The average cardiac index was 4.52 ± 1.29 in the "normal" material and 4.79 ± 1.63 in stenotic cases.

Both groups exhibited tachycardia with an average value for the whole material of 101 ± 21.

Stroke volume showed a fair correlation to BSA with an r value of 0.81 and 0.79 for the normal and stenotic groups, respectively. The equation for the regression line for the whole material was SV = 57.9BSA—8.6. (Fig. 4)

Finally the correlation coefficient for the relationship of cardiac output calculated by the Fick method to the dye technique was found to be 0.86. (Fig. 5)

Discussion. In the absence of vascular shunts the determination of cardiac output by the dye dilution technique employed in the present study may be considered representative for pulmonary as well as systemic output. Information regarding the systemic output in children is relatively scanty in the literature. The best documented

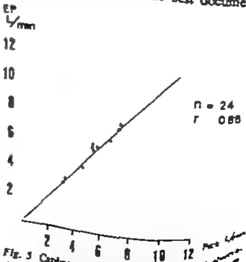

Fig. 5. Cardiac output figures from paired observations by earpiece densitometry (EP) and the direct Fick equation (Fick). Coefficient of correlation 0.86.

data are those published by Brotmacher et al in 1956 (3) and by Cayler et al. in 1963 (4) Both have used modifications of the Fick principle for cardiac output calculation during catheterization of children with various forms of congenital heart lesions There seems to be a general agreement that circulation in children, at least during heart catheterization, is characterised by a hyperkinetic systemic output with cardiac index values (output/M² BSA) in excess of those reported for adults (5 9) The former authors arrived at a figure for systemic output of close to 4 l/min/M² BSA and comment on the fact that the correlation between cardiac output and BSA is not impressive Caylor et al arrive at a somewhat higher figure for cardiac index (4.37 l/min/M² BSA if all of their cases are included) The latter authors, however report an exceedingly high correlation coefficient for the relationship cardiac output/BSA and comment that cardiac index is a meaningful unit also in the growing population The value for mean cardiac index in the present study does not seem to differ significantly from the figures given by Caylor et al and the fact that the mean values for the two groups are so close suggests that the whole material may be treated as one group with respect to the systemic output figures. The fact that stenotic heart lesions do not affect cardiac output significantly is in agreement with findings in adult patients (7)

The finding that the relationship cardiac output/BSA, although better than that reported by Brotacher *et al.*, gives a substantially lower coefficient of correlation than that reported by Caylor et al. deserves commenting. As our method of dye dilution gives a good correlation with values obtained by the Fick method and no systematic differences exist between the values, purely methodological differences are unlikely as explanation. A reasonable explanation would be that our material indeed is less basal than that studied by Caylor et al. This suggestion is partly supported by the fact that there is in both our groups a pronounced degree of tachycardia and that our average cardiac index is higher than that reported by others (3 4) It is not difficult to find a reason for this difference between the materials Whereas it may be presumed that the collection of expired air for Fick analysis as a rule is not begun until a certain degree of basality is reached with the patient accustomed to the procedure no such periods of adjustment were applied in the dye dilution studies reported here Dye curves were as a rule recorded immediately after the completion of the diagnostic catheterization i.e during conditions very like those existing during the pressure measurements and blood gas collection. Only during marked unrest such as crying were dye studies temporarily delayed until the patient calmed down

The finding that stroke volume was better correlated to body dimensions than cardiac output indicates that heart rate is the major denominator in the regulation of systemic outflow in these patients This is in agreement with the concept of cardiac function during anxiety and adrenergic influence in the recumbent patient where the induced tachycardia causes increments in cardiac output with unchanged stroke volume (10 13) Being less "vulnerable" than cardiac output with respect to absence of basality and steady state, stroke volume predicted from BSA by the given regression line equation and multiplied by the actual heart rate might be a better indirect way of assessing cardiac output in the anxious child.

In summary the present results suggest that

1 the child during cardiac catheterization is usually far from basal and observations with respect to pressure and gradients are likely to overemphasize the consequences of a stenotic lesion due to the presence of a state of hyperkinesia, unless flow studies are made

2 it is important to record flow and pressure studies as simultaneously as possible to make the recorded figures commensurable.

3 stroke volume was found to be the parameter best correlated to body dimensions and it is suggested that in the presence of anxiety and unrest SV prediction might be a better indirect way to assess cardiac output.

REFERENCES

1. Barr J W nd Bradley E. C. A calibration device for the earpiece dichromatic densitometer *J Appl Physiol* 25:633, 1968.
2. Bradley E. C. and Barr J W Fore-n-aft triangle formula for rapid calculation of area, *Amer Heart J* 78:673, 1969
3. Brotmacher L. and Deuchar D C. The systemic blood flow in congenital heart disease, with a examination of th validity of the cardia index. *Clin Sci*, 15:441 1956.
4. Cayler G G Rudolph, A. M nd Nadas, A. S. Systemic blood flow in infants and children with and without heart disease. *Pediatrics* 32:186, 1963
5. Cournand, A Riley R. L., Breed, E. S Baldwin, E. and Richards, D W Measurement of cardiac output in man using the technique of catheterization of the right uricle nd entricle. *J Clin Invest*, 24 106, 1945
6. DuBois, D and DuBois, E F Clinical calorimetry A formula t estimate pproximate surface area if height and weight be known *Arch Int Med* 17:863, 1916
7. Gorlin, R., McMillan, I K., Medd, W E., Mathews, M B and Daley R. Dynamics of the circulation in aortic valvular disease. *Amer J Med* 18:855 1955
8. Karlberg, P and Igbom, S. A swedish growth chart. *Acta Paediat Scand* Suppl. 117 p 137 1959
9. McMichael, J and Sharpey-Shafer E. P Cardiac output in man by direct Fick method *Brit Med J* 6.33 1944
10. Rushmer R. F Effects of nerv stimulation and hormones in the heart The role of the heart in general circulatory regulation. Handbook of Physiology Section 2. Vol. I p. 533. Amer Physiol. Soc. Washington D.C., 196_
11. Smith, C., Rowe, R. nd Vlad, P Sedation of children for cardiac catheterization with an ataractic mixture. *Canad Anaesth Soc J* 5.35 1958
12. Wallgren, C. G Hanson, J S Kretzschmar G and Zetterqvist, P Validity of dichromatic ear piece densitometry for quantitative studies in children with shuntfree cardiovascular malformations. *Acta Paediat Scand* 1975 This Suppl.
13. Weissler A. M Leonard, J J and Warren, J V Effect of posture nd atropine on cardiac output. *J Cli Invest* 36 1656, 1957

III. EVALUATION OF THE FORWARD TRIANGLE AREA IN DYE CURVES FROM INFANTS AND CHILDREN STUDIED BY EARPIECE DENSITOMETRY

by

C. GÖRAN WALLGREN

ABSTRACT: Onehundred and six dye curves recorded by earpiece densitometry in shunt-free children were analysed with respect t the spatial relationships between the forward triangle and the area under the total primary dye curve. It is suggested that the relationship between these two areas, the forward triangle factor should be 0.32 for studies in children with the use of dichromatic earpiece densitometry

KEY WORDS Earpiece densitometry forward triangle factor

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Whereas the indicator dilution technique readily lends itself to cardiac output calculations by the Stewart Hamilton equation in patients without central recirculation, the presence of left-to-right shunts interferes with the area calculation of the primary curve and thus invalidates the tracing for quantitative use

To overcome this shortcoming of the method in instances with rapid central recirculation various modifications of the area calculation have been put forward (2, 6) The most commonly used is that of Hetzel et al. (6) who analysed the area of the "forward triangle" i.e. the area defined as peak concentration build-up time x peak concentration / 2 as a fraction of the total area under the extrapolated primary curve That study indicated a fairly constant relationship between these two areas and they suggested a total area calculation based on a forward triangle (FT) fraction of 0.37

It has later been shown that this fraction yields different values if the injection site is changed (1) and a different value has been found in densitometric studies in newborn infants with central injection and sampling (4) In view of the fact that the presently used method differs substantially from that used by the above groups and the fact that the material with respect to age distribution is entirely different, it was deemed important to evaluate what forward triangle fraction ought to be used for area calculation in the presence of left to-right shunt in infants and children.

Material and methods 106 dye dilution curves from 13 patients without signs of shunt lesion were analysed. The basic heart lesion was mostly mild obstruction to ventricular outflow in postoperative patients. The subjects varied in age between 4 and 18 years (mean = 7.2). There were no signs of cardiac decompensation or valvular regurgitation in the material Two mg of Cardiogreen were injected into the main pulmonary artery and the dilution curve was recorded by earpiece densitometry as has been described in detail elsewhere (7)

The evaluation was usually made on randomly selected curves but care was taken to include only tracings that were considered technically

good. Curves with drifting base lines and artifacts due to movement of the patient were ruled out. In all of the evaluated tracings the onset of the primary curve was distinct and the peak concentration build-up time could be measured with an accuracy of 0.5 mm at a paper speed of 0.5 cm/sec. Peak concentration deflection was in excess of 100 mm in all instances. The area under the primary dilution curve was calculated by planimetry after due extrapolation of the curve s exponential decay portion to near zero.

Results. The forward triangle fraction amounted to 0.32 ± 0 03 range 0.26—0 41 There was as great variation in the value from different curves in the same patient as between patients. There was no indication of an age dependent variability of the forward triangle fraction but the small number of patients as well as the age distribution of the material make it unsuitable for evaluation of this relationship

Discussion. The forward triangle factor originally suggested by Hetzel et al. (6) has subsequently been altered for use with central injection in the adult (1) and with central injection and sampling in the newborn infant (4) Although it is difficult to state which parameter affects the spatial relationship between the forward triangle area and the total area under the primary dye curve, it seems as if both methodological differences and the age of the patient may have bearings on this relationship

Although dilution curves recorded by earpiece densitometry have been demonstrated to possess the same overall spatial characteristics as those recorded by cuvette densitometry (3), it may be questioned whether the lower forward triangle fraction in the present investigation may be attributed to methodological differences inherent in the earpiece set-up The fact that recordings by earpiece densitometry reflect the dye concentration in an infinite number of small vessels rather than the situation pertaining in a major artery may conceivably have a bearing on the time concentration relationship A prolongation of the wash-out of dye from the studied tissue should give a longer decay portion of the curve and consequently result in a smaller FT fraction. In order to evaluate this possibility simultaneously made recordings by earpiece and cuvette technique in the same patient were evaluated for possible differences with respect to the spatial relationships between forward triangle area and the rest of the dye curve. No systematic difference in this respect was found in tracings from 5 patients 15—17 years old.

Another possibly more likely explanation to the lower FT value reported here is the composition of the present material with respect to age It is well known that infants and children have characteristically faster circulation than adult man, and this may well influence the spatial relationships of the various curve areas. Although the present material has not indicated an age dependent factor the significance of this is very limited, as stated, and a differently planned investigation is needed to study this matter further

Although the forward triangle method makes it possible to use dye curves for quantitative use in the presence of central recirculation, it should be kept in mind that the great individual variability of the FT factor introduces an additional error to the method, which of necessity ought to render it less sensitive than the conventional Stewart Hamilton technique (5) The fact that in rapidly repeated dye dilution curves the reproducibility has been found amazingly high (4) does not disprove this assumption

REFERENCES

1 Benchimol, A., Dimond, E. G Carvalho, F R. and Robert, M W The forward triangle formula for calculation of cardiac output. *Amer J Cardiol* 12.119 1963

2 Dow P Dimensional relationships in dye-dilution curves from humans and dogs, with an empirical formula for certain troublesom curves. *J Appl Phy iol* 7 399 1954

3 Gabe, I and Shillingford, J The photoelectric earpiece technique for recording dye dilution curves *Brit Heart J* 23.271 1961

4. Hanson, J. S., Arcilla, R. A., Oh, W. Wallgren, G. and Lind, J. Dye dilution. Principles and techniques. *Acta Paediat Scand* Suppl. 179 1967
5. Hanson, J. S. and Tabakin, B. S. Simultaneous and rapidly repeated cardiac output determinations by dye-dilution method. *J Appl Physiol*, 19:275 1964
6. Hetzel, P. S., Swan, H. J. Ramirez de Arellano A. and Wood, E. H.. Estimation of cardiac output from first part of arterial dye-dilution curves. *J Appl Physiol* 13:92, 1958
7. Wallgren, C. G. Hanson, J. S., Kretzschmar G. and Zetterqvist, P.. Validity of dichromatic earpiece densitometry for quantitative studies in children with shuntfree cardiovascular malformations. *Acta Paediat Scand* 1975 This Suppl.

IV EVALUATION OF DICHROMATIC EARPIECE DENSITOMETRY IN CHILDREN WITH LEFT TO-RIGHT SHUNTS

by

C. GÖRAN WALLGREN GÜNTER KRETZSCHMAR and PER ZETTERQVIST

ABSTRACT Earpiece densitometry was performed in 60 infants and children with left-to-right cardiovascular shunts. The method was found to possess high diagnostic sensitivity with respect to identification of the left-to-right shunt. Earpiece densitometry was in this respect clearly superior to conventional method using oxygen saturation figures. Quantitation of pulmonary blood flow by both densitometric and oxygen content technique in small number of patients indicates that the dye dilution technique gives values somewhat in excess of the Fick method. It is concluded that quantitation of the magnitude of the left-to-right shunt and pulmonary blood flow is disturbed by the fact that indicator material is recirculated before the ascending limb of the primary curve is fully inscribed.

KEY WORDS Earpiece densitometry left-to-right shunt.

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Although indicator dilution techniques are considered to be very reliable tools for the iden tification of cardiovascular shunts (5 8, 9) their use for truly quantitative work with evaluation of cardiac output in the presence of central shunts meets with a number of technical difficulties.

A major prerequisite for cardiac output determination by indicator dilution technique is that the entire injected amount of indicator ma terial participates only once in the buildup of the primary" curve This invalidates the dilution curve for quantitative use in the presence of right-to-left shunts between the sites of injection and sampling because of indicator loss. It also makes the presence of left-to-right shunts problematic for the area calculation of the primary curve a parameter necessary for the calculation of cardiac output according to the Stewart-Hamilton technique. This latter problem is due to the fact that recirculation of shunted blood containing indicator material distorts the exponential decay portion of the primary curve and consequently interferes with the area calculation.

This shortcoming of the indicator dilution technique, particularly evident in many in stances of congenital heart disease, has prompted modifications of the area calculation method. The "forward triangle" technique suggested by Hetzel et al. (4) is presently being widely used in instances of left to-right shunts. The method approximates the total area under the primary dilution curve from the first part of the curve alone. This part has been shown to bear a fairly constant relationship to the total area and this relationship, the forward triangle factor was originally computed for use with cuvette densitometry in adult patients It has subsequently been modified for the use with earpiece densitometry in a pediatric population (1)

The present investigation was undertaken in an effort to evaluate the discriminating power

of earpiece densitometry with respect to the presence of left-to-right shunts as well as its applicability to semiquantitative and/or quantitative evaluation of shunt flow and pulmonary blood flow in children with congenital heart lesions and central recirculation.

Material. Sixty consecutive patients with left to-right shunts constitute the subject material for the present investigation. Forty-one had their shunt at the ventricular level and the remaining 19 at the atrial level. There were 35 girls and 25 boys with age variations between 5 months and 15 years (mean 7.2 years) The shunt was estimated by oxygen content figures to be small (Q_p/Q 1.5 or less) in 20 patients, moderate ((Q /Q 1.5—2) in 23 and big (Q / Q in excess of 2) in the remaining 17 patients. Among the 20 patients with small shunts, 5 had no significant oxygen step-up between mixed venous and pulmonary arterial blood samples, but a typical VSD murmur indicated the presence of a ventricular shunt beyond the discriminating power of the oxygen method. None of the patients was in cardiac failure at the time of investigation and there were no signs of valvular incompetence

An additional group of 30 infants and children without signs of central shunts was used for the study of various pertinent characteristics of the primary curve.

Methods Densitometry The earpiece densitometric technique previously described in detail (11) was used throughout. Injection of 2 mg of Cardiogreen was made into the main pulmonary artery and whenever possible also from the left atrium to evaluate the pulmonary circulation time (PCT) The dilution curves were recorded from the left ear pinna with care taken to assure good perfusion of the recording site (11) A Waters D 401 densitometer was used throughout and the recording instrument had a response time of less than 0.5 sec for full scale deflection. The technique of earpiece calibration has been described in detail elsewhere (11)

Identification of left-to-right shunts Visual recognition of the distortion of the curve's decay portion by recirculation served to identify the presence of left-to-right shunts

Relative quantitation of shunt size The assessment of the relative magnitude of the shunt (QP/QS) from the dilution curve was achieved by comparing peak concentration with dye concentrations at multiples of the concentration build-up time according to Carter et al (2)

Absolute quantitation of shunt size and pulmonary blood flow The forward triangle method of area calculation was used in all instances and the FT factor suggested by the authors for use with earpiece densitometry in infants and children was employed (12)

Pulmonary circulation time. In every instance where the left atrium was entered PCT was estimated as the difference in appearance time between pulmonary arterial and left atrial injections

Oxygen methods Oxygen saturation of blood samples was measured by direct spectrophotometry (American Optical Micro Sample Oximeter) A step-up in oxygen content in excess of 1 vol% between the superior caval venous blood and that of the pulmonary artery was taken to indicate the presence of a left to-right shunt. The ratio QP/QS was assessed by standard shunt equations. Expired air was collected in 9 patients simultaneous with dye dilution recordings for the assessment of pulmonary blood flow by the Fick method. Oxygen saturation of pulmonary venous blood, whenever not assessable, was assumed to be 97 % in all instances.

RESULTS

Identification of left to-right shunts: In every instance of central recirculation verified by oxymetric data the dye dilution curve showed the characteristic appearance of recirculated indicator material While large shunts usually gave a flat, slowly descending concentration decay smaller shunts exhibited an early more distinct breaking point in the exponential decay of the curve (Fig. 1) As a rule, the presence of a left

quantitation of shunt flow a distinct tendency in some cases to an overestimate by the dye method. This was particularly true in small subjects with big shunts where the pulmonary blood flow assessment by the FT method gave unreasonably high values.

Pulmonary circulation time In the 30 patients where the left atrium was entered PCT averaged 2 45 ± 1.25 sec.

Discussion. It has long been recognized that the oxygen method for shunt identification is a fairly insensitive diagnostic tool (1 3 13) Methodological errors in oxygen content analyses, variations in oxygen content in samples from the same site, together with difficulties in assessing truly mixed venous blood oxygen content, reduces the discriminatory power of the method The fact that blood samples from sites proximal and distal to the shunt are rarely taken simultaneously further reduces the methodological accuracy

A number of indicator dilution techniques have been shown to possess superior shunt identification properties (5 8) The more or less instantaneous character of the dye dilution technique combining the facility of rapid checks

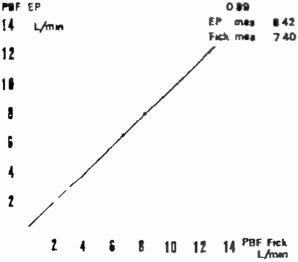

Fig 2 Pulmonary blood flow measured by earpiece densitometry (EP) related to measurements by the oxygen equation (Fick) in 9 subjects with left-to-right shunt (QP/QS 1—7). The area calculation of the dye curve was accomplished by use of forward triangle factor of 0.32. Coefficient of correlation 0 89

of reproducibility with the impressive capacity of the method to supply additional informations regarding the status of the circulatory system, has made the densitometric technique a very attractive alternative Earpiece densitometry evidently shares the advantages of the conventional densitometric technique with respect to shunt discriminating power The fact that the method is "atraumatic" to the patient and technically easy to perform further emphasizes that it is the method of choice for the pediatric cardiologist whenever there is a question of identifying small or "questionable" shunts, be they left-to-right or right-to-left

Although advantageous for qualitative use the earpiece densitometric technique seems less reliable for evaluation of the magnitude of the left to-right shunt. The Carter formula for assessing the QP/QS ratio was originally obtained from studies with cuvette densitometry in predominantly adult patients Thus formula like any other suggested formula for quantitative evaluation of flow from one single injection site, presupposes that peak concentration of the dye curve is not affected by recirculating indicator material, i e PCT must be longer than the peak concentration build-up time (BUT)

In order to evaluate the possibility of interference with recirculating dye in the descending portion of the dilution curve the relationship PCT/BUT had to be studied specifically BUT was measured in curves from 30 shuntfree children, and care was taken to keep the age distribution as similar as possible to that of the shunt material Concentration build-up time in this control group averaged 3 [illegible] ± 0 [illegible] sec as compared to a mean PCT of 2 45 sec. for the shunt patients. Provided that the two groups are comparable with respect to these time intervals, which seems an acceptable assumption, recirculation is likely to occur before peak concentration is reached in most of the studied patients

Evaluating the possible mechanisms responsible for this situation it may be questioned whether it is the shorter pulmonary circulation time in young subjects or a prolongation of the BUT inherent in the earpiece densitometric

method that should be blamed. To analyse this question further BUT was assessed from simultaneous earpiece and cuvette recordings in 10 shunt free children, the cuvette densitometric tracings being recorded at a withdrawal rate of *25 ml/min. The average BUT* estimated from the cuvette tracings was on an average 15 per cent shorter than corresponding value for ear piece densitometry but was still well in excess of the average PCT for the shunt material.

Although the characteristics of the earpiece recording thus enhances the chances of recirculation occurring before peak concentration is reached it is likely that the short PCT in infants and children plays a major role in this respect. It would consequently seem advisable to document a PCT/BUT ratio of more than unity before dye curves in this age group are used for quantitative evaluation of left-to-right shunts.

In the presence of a PCT/BUT ratio of less than unity in most of the studied patients it is astonishing that the forward triangle method agrees so well with figures obtained by the Fick principle for pulmonary blood flow It is in this context important to realise that the impact of recirculating indicator material on the upstroke part of the curve is related both to the size of the shunt and thereby the amount of recirculated dye, and also to the magnitude of the PCT/BUT ratio The concentration/time relationship of the recirculated dye yields a flatter and more prolonged curve, the first part of which may have negligible influence on the peak concentration. This is particularly true if the shunt (and thus the amount of recirculated dye) is small and the *PCT/BUT ratio is slightly* less than unity i.e. recirculation does occur close to the peak concentration. This reasoning may well be applicable to the 9 instances in which densitometric and Fick estimates were compared. These patients were older than the average of the group and suffered from left-to-right shunts than were judged as moderate in most cases.

The Carter formula, which also takes into consideration concentration levels at multiples of BUT should by necessity be more susceptible to the effect of early recirculation than area calculation by the FT formula. The effect of recirculation shortly before the peak concentration would result in a relatively unaffected peak of the primary curve while concentrations at *multiples of BUT would be relatively higher* due to recirculating dye The formula would under these conditions give overestimates of the QP/QS ratio.

The reports of Nakamura et al (10) and of Keck et al. (6) both claiming acceptable correlation between the densitometric shunt formula and the oxygen content equation are contradictory to the present findings Although the cited authors have used different indicator material as well as different densitometric equipment, methodological factors can hardly be responsible for the different interpretations. It is more likely then that differences with respect particularly to age distribution of the subjects studied account for the better correlation between the methods in their reports. It should also be kept in mind that although these authors indicate an overall good correlation between the densitometric and oxygen method for relative shunt estimates, the difference could amount to as much as 50 % in the individual patient.

The new formula suggested by Krovetz et al (7) to overcome the impact of recirculation in the upstroke part of the dye curve in patients with very rapid pulmonary circulation requires left-sided indicator injection and may be of value in instances where the left atrium may be entered In the majority of our patients, however this approach was not possible

A more detailed analysis of the influence of recirculation on the area calculation by the forward triangle method is required to evaluate to what extent the present method or modifications of it may be reliable for quantitation of pulmonary blood flow and the magnitude of the left-to-right shunt in patients in the pediatric age group A model experiment is presently being set up in this laboratory with the hope that some problems with unfavourable PCT/BUT relationships in instances of central recirculation may be solved.

REFERENCES

1. Barrat-Boyes, B. G. and Wood, E. H. The oxygen saturation of blood in the venae cavae, right heart chamber and pulmonary vessels in healthy subjects. *J Lab Clin Med*, 50:93, 1957
2. Carter, S. A., Bajec, D. F., Yannicelli, E. and Wood, E. H. Estimation of left-to-right shunt from arterial dilution curves. *J Lab Clin Med* 55:77, 1960
3. Gorlin, G. Normal variation in venous oxygen content. In Methods in Medical Research. The Yearbook Publisher Inc. Chicago, 1958
4. Hetzel, P. S., Swan, H. J. C., Ramirez de Arellano, A. A. and Wood, E. H. Estimation of cardiac output from first part of arterial dye dilution curves. *J Appl Physiol* 13:92, 1958
5. Hyman, A. L., Myers, W. Hyatt, K. DeGraff, A. G. and Quiros, A. C. A comparative study of the detection of cardiovascular shunts by oxygen analyses and indicator dilution methods. *Ann Int Med* 56:535, 1962.
6. Keck, E. W. DelaRiega, E. and Wolf, D. Zur relativen Grossenbestimmung eines Links-Rechts-Shunt mittels der Farbstoff Verdunnungsmethode unter Verwendung der Ohreinheit. *Z Kreisl Forsch* 53..., 1963
7. Krovetz, J. L. and Gessner, I. A new method utilizing indicator-dilution techniques for estimation of left-to-right shunts in infants. *Circulation*, 3: 772, 1965
8. Mook, G. A. and Zijlstra, W. G. Quantitative evaluation of intracardiac shunts from arterial dye dilution curves. Demonstration of very small shunts. *Acta Med Scand* 170:703, 1961
9. Morrow, A. G. Sanders, R. J. and Braunwald, E. The nitrous oxide test. An improved method for detection of left-to-right shunts. *Circulation*, 5:284, 1958
10. Nakamura, T. Katori, R., Watanabe, T. Miyazawa, K., Murata, M. Oda, J. and Ishikawa, K. Quantitation of a left-to-right shunt from a single earpiece dye dilution curve. *J Appl Physiol* ...: 1156, 1967
11. Wallgren, C. G. Hanson, J. S., Kretzschmar, G. and Zetterqvist, P. Validity of dichromatic ear piece densitometry for quantitative studies in children with shuntfree cardiovascular malformations. *Acta Paediat Scand* 1975. This Suppl.
12. Wallgren, C. G. Evaluation of the forward triangle area in infants and children studied by earpiece densitometry. *Acta Paediat Scand* 1975. This Suppl.
13. Warren, E. W. and Stead, E. A. The cardiac output in man. A study of some errors in the method of right heart catheterization. *Amer J Physiol* 154:458, 1946

EXERCISE STUDIES IN CHILDREN WITH CONGENITAL HEART DISEASE: AN EARPIECE DENSITOMETRIC INVESTIGATION

by

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ABSTRACT. Twenty-three patients have been studied by exercise testing during right heart catheterization. Cardiac output was measured by the earpiece densitometric technique before, during and after the exercise period. It is concluded that the earpiece densitometric technique in conjunction with exercise testing offers an attractive alternative for the study of pressure and flow characteristics in children with congenital heart disease.

KEY WORDS. Earpiece densitometry, congenital heart disease, exercise test.

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Exercise testing is usually performed in order to evaluate the capacity of the circulatory system to supply an increased oxygen transport. It is, however, also the most physiological way of obtaining information regarding the hemodynamic situation during increased blood flow. The application of hemodynamic investigations during graded exercise has become a valuable diagnostic tool, particularly with respect to the appraisal of the severity of local obstructions to blood flow but also for the study of characteristics of the resistance in a particular vascular compartment.

The earpiece technique for obtaining dye dilution curves has earlier been evaluated for quantitative use at rest in children with various types of congenital heart disease (11, 12, 14). In view of the ease with which the method is applied to the patient it ought to lend itself readily to studies of the circulatory dynamics also during exercise. It should present a practical method for cardiac output evaluation in a situation where conventional methods, including collection of expired air or arterial cannulation for cuvette densitometry, are likely t[illegible] considerably more inconvenient for th[illegible]

The following investigation was [illegible] with these viewpoints in mind, and [illegible] of the study included not only eval[illegible] the densitometric method per se during ex[illegible] studies in children, but also study of [illegible] sponse of the cardiovascular system [illegible] cise in various types of congenital heart [illegible]

Material and methods: Twenty-three pa[illegible] ranging in age from 6 to 21 years (mea[illegible]) constitute the subject material [illegible] investigation. The subjects could be d[illegible] into three groups with respect to the car[illegible] vascular status. Eight patients considered [illegible] mal from a cardiovascular viewpoint con[illegible] the first group. These patients had either surg[illegible] ally corrected heart defects without signs of [illegible] sidual pathology or unusually loud physiolog[illegible] cal murmurs undergoing catheterization to r[illegible] out cardiac pathology. The second group w[illegible] made up of 7 children with pulmonic steno[illegible] with systolic gradients across the pulmonic val[illegible] at rest between 15 and 60 mm Hg. [illegible]